British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

Asthma: diagnosis, monitoring and chronic asthma management (update)

[P] Evidence reviews for drug classes for initial asthma management

BTS/NICE/SIGN collaborative guideline NG245

Evidence reviews underpinning recommendations 1.6.2, 1.7.1, 1.8.1, 1.9.1, 1.9.2, 1.9.3, 1.9.4, 1.9.5 and 1.9.6 and research recommendations in the guideline

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Developed by BTS, NICE and SIGN

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Contents

1 Pharmacological management of Asthma in people who are treatment-naive or receiving SABA-only 5
1.1 Review question 5
1.1.1 Introduction 5
1.1.2 Summary of the protocol 5
1.1.3 Methods and process 6
1.1.4 Effectiveness evidence 7
1.1.5 Summary of studies included in the effectiveness evidence 7
1.1.6 Summary of the effectiveness evidence in young people/adults ≥12 years 16
1.1.7 Economic evidence 29
1.1.8 Summary of included economic evidence 30
1.1.9 Economic model 31
1.1.10 Unit costs 32
1.1.10.1 Cost-comparison analysis 33
1.1.11 Evidence statements 35
1.2. The committee's discussion and interpretation of the evidence 35
1.3 References 42
Appendices 45
Appendix A – Review protocols 45
Appendix B – Literature search strategies 55
Appendix C – Effectiveness evidence study selection 66
Appendix D – Effectiveness evidence 67
Appendix E – Forest plots 208
Appendix F – GRADE tables 227
Appendix G – Economic evidence study selection 240
Appendix H Economic evidence tables 241
Appendix I – Excluded studies 243
Appendix J – Research recommendation 269

1 Pharmacological management of Asthma in people who are treatment-naive or receiving SABA-only

1.1 Review question

What is the most clinically and cost-effective drug class or combination of drug classes (short-acting beta agonist [SABA] prn, SABA prn plus regular inhaled corticosteroid [ICS], or ICS plus SABA / long-acting beta-agonist [LABA] combination inhaler prn) for the management of asthma in people who are treatment-naïve or receiving SABA alone?

1.1.1 Introduction

When people first present with asthma it is not possible ot predict how much treatment they will need to achieve control of the disease and there has not been universal agreement about the optimum intensity of first line treatment. Some advocate starting everyone on inhaled corticosteroids (ICS) with varying opinions about the correct starting dose, while others think it better to start with a short-acting beta-agonist (SABA) used as required, at least in people who do not present with obviously severe symptoms. Recently it has been suggested that it would be better to start with a combination inhaler containing an ICS and formoterol, a fast-onset long-acting beta-agonist (LABA), used only when needed. The purpose of this review is to compare these options.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion: People with a diagnosis of asthma that: • Include those on no asthma therapy • Include those on short acting beta agonist as sole asthma therapy (no limit on duration) • have not yet received preventer/maintenance (inhaled corticosteroids) treatment Strata by age: • Infants and children <5 years old • Children 5-11 years old • Young people and adults ≥12 years old Exclusion: • People who have received preventer (inhaled corticosteroid) treatment • People with severe asthma

Interventions	• Short-acting beta agonist [SABA] prn
	  ○ Salbutamol
	  ○ terbutaline
	• SABA prn plus regular inhaled corticosteroid [ICS]

	○ budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) • ICS combination inhaler prn ○ Any ICS / formoterol combination inhaler ○ Any ICS with any fast-acting SABA combination (salbutamol, terbutaline) Minimum duration of study treatment: 8 weeks
Comparisons	Interventions to one another
Outcomes	• Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at 3-5 and ≥6 months) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at 3-5 and ≥6 months) • Reliever/rescue medication use (continuous outcome at ≥3 months) • Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). • Adverse events ○ Linear growth (continuous outcome at ≥1 year), ○ Pneumonia frequency (dichotomous outcome at ≥3 months) (including lower respiratory and general, in that order, respiratory tract infections, but not including upper respiratory tract infections) ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months) ○ Bone mineral density (continuous outcome at ≥6 months) Inflammatory markers; exhaled nitric oxide (FeNO) (continuous outcome at ≥8 weeks)
Study design	• RCT • Systematic reviews of RCTs

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted to identify randomised controlled trials comparing the effectiveness of two or more of; SABA, ICS+SABA and ICS combination inhalers in people diagnosed with asthma who were yet to receive treatment or had received SABA as a sole therapy.

Twenty randomised controlled trials were included in this review, thirteen (Bateman, et al., 2021, Beasley, et al., 2019, Berger, et al., 2002, Boonsawat, et al., 2008, Chuchalin, et al., 2008, Galant, et al., 1996, Hoshino, et al., 1998, Jones, et al., 1994, Kemp, et al., 2000, Kerwin, et al., 2008) (Nathan, et al., 1999, O'Byrne, et al., 2014, Sheffer, et al., 1996) in adults, two in children (Nayak, et al., 2002, Ruff, et al., 2003) and five in infants (Chavasse, et al., 2001, Papi, et al., 2009, Schokker, et al., 2008, Teper, et al., 2004, Teper, et al., 2005). Studies in adults and infants investigated SABA, ICS+SABA and ICS combination inhalers. Studies in children investigated SABA compared to ICS+SABA. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

Twelve potentially relevant Cochrane systematic reviews were identified in the searching process. These reviews were assessed as full texts and were excluded for reasons outlined in Appendix I. Most reviews were excluded due to including studies that contained participants that were not steroid naïve, or included interventions that were not relevant to this review protocol. All Cochrane systematic reviews were cross-checked for relevant studies, although no further studies were identified.

See the excluded studies list in Appendix I.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of the studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bateman 2021 (SYGMA) (Bateman et al., 2021)	Trial with three arms: **SABA** (placebo plus 0.5mg terbutaline as needed) **ICS+SABA** (twice-daily 200 mcg budesonide plus 0.5mg terbutaline as needed) **ICS combination inhaler** (200 mcg budesonide/6 mcg formoterol as needed)	≥12 years (mean age 38 years, SD 16)with asthma in need of GINA step 2 treatment (uncontrolled on SABA as needed) 2-4 week run in period where participants received terbutaline (0.5 mg) as needed for symptoms. N=3640	All outcomes assessed at 52 weeks: Severe asthma exacerbations Mortality Asthma control Lung function Adverse events	Funded by AstraZeneca. Secondary analysis of SYGMA 1 and 2 which combined data from both studies in only those who were steroid naïve at recruitment.

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 52 weeks	Treatment status: SABA as needed Asthma history: not reported Multinational study		
Beasley 2019 (Beasley et al., 2019)	Trial with three arms: **SABA** (100mcg albuterol, two inhalations from pMDI) as needed **SABA+ ICS** (100 mcg albuterol, two inhalations from pMDI as needed + 200mcg budesonide, one inhalation twice per day) **ICS combination inhaler** (6 mcg formoterol/200 mcg budesonide, single inhalation as needed) Follow-up: 52 weeks	≥12 years (18-75 years) with asthma diagnosis (mean age, SD: SABA - 35.8y, 14.0; SABA+ICS – 34.9y, 14.3; ICS combination – 36.0, 14.1) N=668 Treatment status: SABA as the sole asthma therapy in the previous 3 months; use of SABA on at least two occasions, but on an average of two or fewer occasions per day in the previous 4 week Asthma history: not reported New Zealand, United Kingdom, Italy and Australia	All outcomes assessed at 52 weeks: Severe asthma exacerbations Reliever medication use Asthma control Lung function Inflammatory markers	Funded by AstraZeneca
Berger 2002 (Berger et al., 2002)	**ICS+ SABA** (250mcg fluticasone propionate once per day plus SABA as needed)	≥12 years (age range 12-74, mean 33 years) with asthma defined by ATS criteria requiring	Severe asthma exacerbations Reliever/rescue medication use Lung function [FEV1 (L) and PEF]	Supported by GlaxoSmithKline Downgraded for population

Study	Intervention and comparison	Population	Outcomes	Comments
	SABA (placebo inhaler once per day plus SABA as needed) Follow-up: 12 weeks	pharmacotherapy for at least 6 months (2 week run-in period) N=408 Treatment status: receiving SABA Asthma history: not reported USA		indirectness (participants could have been receiving theophylline prior to study entry)
Boonsawat 2008 (Boonsawat et al., 2008)	**ICS+SABA** (100mcg fluticasone propionate once per day plus salbutamol as needed) **SABA** (placebo plus salbutamol as needed) Follow-up: 12 weeks	≥12 years (12-79 years) diagnosed with asthma for at least 6 months. (2-week run-in period where all participants had their current therapy discontinued and received salbutamol as-needed) N=309 Treatment status: receiving SABA Asthma history: not reported International	Severe asthma exacerbations Lung function (PEF) Adverse events	Supported by GlaxoSmithKline
Chavasse 2001 (Chavasse et al., 2001)	**SABA+ICS** (50mcg fluticasone propionate, three Inhalations twice per day, plus SABA as needed) **SABA** (placebo inhaler, one inhalation twice per day plus SABA as needed) Follow-up: 12 weeks	Infants (aged 3 to 12 months) with history of persistent or recurrent wheeze or persistent cough (2 week run-in period) N=37	Reliever/rescue medication use	Supported by GlaxoWellcome

Study	Intervention and comparison	Population	Outcomes	Comments
		Treatment status: not reported Asthma history: not reported UK		
Chuchalin 2008 (Chuchalin et al., 2008)	**SABA+ICS** (100mcg fluticasone propionate, one inhalation per day, plus salbutamol as needed) **SABA** (placebo twice per day plus salbutamol as needed) Follow-up: 52 weeks	≥12 years (12-79 years) diagnosed with asthma for at least 6 months. (2 week run-in period) N=1285 Treatment status: receiving SABA Asthma history: not reported International	Lung function (PEF) Adverse events Pneumonia (RTIs)	Supported by GlaxoSmithKline
Galant 1996 (Galant et al., 1996)	**SABA + ICS** (25 or 50 mcg fluticasone propionate, two inhalations twice per day plus SABA as needed – 2 trial arms combined) **SABA** (placebo inhaler, two inhalations twice per day plus SABA as needed) Follow-up: 12 weeks	≥12 years (range 12-75 years, mean 30 years) with stable reversible asthma (1 week run-in period where participants received placebo ICS and theophylline) N= 264 Treatment status: receiving SABA Asthma history: not reported USA	Reliever/rescue medication use Adverse events	Supported by Glaxo Research Institute
Hoshino 1998	**SABA+ ICS** (400 mcg beclomethasone	≥12 years (16-48 years) with	Reliever/rescue medication use	Supported by Schering-

Study	Intervention and comparison	Population	Outcomes	Comments
(Hoshino et al., 1998)	dipropionate, one inhalation twice per day plus salbutamol as needed) **SABA** (placebo twice per day plus salbutamol as needed) Follow-up: 6 months	asthma diagnosed according to ATS criteria N=24 Treatment status: not reported Asthma history: not reported Japan	Lung function (FEV1 % predicted and PEF)	Plough Foundation
Jones 1994 (Jones et al., 1994)	**SABA+ ICS** (400mcg budesonide once per day or 200 mcg twice per day plus SABA as needed (3 study arms combined) **SABA** (placebo inhaler, twice per day with SABA as needed) Follow-up: 12 weeks	≥12 years (12-70 years) with mild/moderate stable asthma (1 week run-in period) N=340 Treatment status: receiving SABA Asthma history: mixed UK	Reliever/rescue medication use Lung function (PEF) Adverse events Pneumonia (RTIs)	
Kemp 2000 (Kemp et al., 2000)	**SABA+ ICS** (100 or 200 mcg mometasone furoate, two inhalations in the morning (200 or 400 mcg) or 100 mcg as two inhlations twice per day (400 mcg) plus SABA as needed (3 arms combined) **SABA** (placebo inhaler , two inhalations twice per day plus SABA as needed) Follow-up: 12 weeks	≥12 years Adults and adolescents with an asthma history of ≥6 months (mean age, SD: SABA+ICS- 30, 12; SABA- 32, 15) N=306 Treatment status: receiving SABA Asthma history: not reported	Lung function (FEV1 and PEF) Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
		USA		
Kerwin 2008 (Kerwin et al., 2008)	**SABA+ICS** (250mcg fluticasone propionate once per day plus SABA as needed) **SABA** (placebo inhaler once per day plus SABA as needed) Follow-up: 12 weeks	≥12 years(12-85 years) (2 week run-in period) N=424 Treatment status: receiving SABA Asthma history: not reported USA and Canada	Severe asthma exacerbations Reliever/rescue medication use Lung function (FEV1 and PEF) Adverse events	Funded by GlaxoSmithKline
Nathan 1999 (Nathan et al., 1999)	**SABA+ICS** (84mcg beclomethasone dipropionate four times per day plus SABA as needed) **SABA** (placebo inhaler plus SABA as needed) Follow-up: 6 months	≥12 years. (mean age, SD: SABA+ICS – 29.9, 1.1; SABA – 29.1, 1.1) N=258 Treatment status: receiving SABA Asthma history: not reported USA	Severe asthma exacerbations Reliever/rescue medication use Lung function (FEV1)	Funded by Glaxo Wellcome Population indirectness: participants could have been receiving intranasal corticosteroids or intranasal cromolyn sodium at screening and were allowed to maintain this treatment at a constant dose.
Nayak 2002 (Nayak et al., 2002)	**SABA+ ICS** (40 or 80mcg beclomethasone dipropionate, one inhalation twice per day plus SABA as needed) **SABA** (placebo inhaler , one inhalation twice per day plus SABA as needed) Follow-up: 12 weeks	Children aged 5-12 years with stable, moderate, symptomatic asthma for ≥6 months (2 week run-in period) N=353 Treatment status: receiving SABA Asthma history: not reported USA	Adverse events Adrenal insufficiency (subset of 20 participants)	Sponsored by 3M Pharmaceuticals

Study	Intervention and comparison	Population	Outcomes	Comments
O'Byrne 2014 (O'Byrne, et al., 2014)	**SABA+ICS** (50 mcg fluticasone furoate, one inhalation once daily plus SABA as needed) **SABA** (placebo inhaler, one inhalation once daily plus SABA as needed) Follow-up: 12 weeks	≥12 years with asthma diagnosis for ≥12 weeks. Mean age, SD: SABA+ICS – 36.7, 16.2; SABA – 33.8, 13.9 . N=222 Treatment status: receiving SABA Asthma history: not reported Mexico, Peru, Russia and USA	Severe asthma exacerbations Quality of life Asthma control Reliever/rescue medication use Lung function (FEV1 and PEF) Adverse events Pneumonia	Funded by GlaxoSmithKline Population indirectness: participants could have been treated with SABA, LTRAs or a combination prior to screening.
Papi 2009 (Papi et al., 2009)	**SABA+ICS** (400 mcg beclomethasone, one inhalation twice per day plus salbutamol as needed **ICS combination inhaler** (800/1600 mcg beclomethasone/salbutamol, taken as needed **SABA** (2500 mcg salbutamol taken as needed) Follow-up: 12 weeks	Infants aged 1-4 years with frequent wheezing referred to a specialist asthma unit for further investigation N=276 Treatment status: Not reported Asthma history: No previous exacerbations Location not reported	Reliever/rescue medication use (day and nighttime use) Adverse events	Funded by Chiesi Farmaceutici
Ruff 2003 (Ruff et al., 2003)	**SABA+ICS** (50 or 100 mcg one inhalation twice per dau fluticasone propionate plus SABA as needed (two trial arms combined)	Children aged 6-12 years with mild to moderate symptomatic asthma for ≥6 months. N=319	Severe asthma exacerbations Lung function (PEF) Adverse events Pneumonia	Sponsored by 3M Pharmaceuticals

Study	Intervention and comparison	Population	Outcomes	Comments
	SABA (placebo one inhalation twice per day plus SABA as needed) Follow-up: 12 weeks	Treatment status: receiving SABA Asthma history: not reported USA		
Schokker 2008 (Schokker et al., 2008)	**SABA+ICS** (50mcg one inhalation twice per day fluticasone propionate plus SABA as needed) **SABA** (placebo one inhalation twice per day plus SABA as needed) Follow-up: 6 months	Children aged 1-5 years N=96 Treatment status: not reported Asthma history: not reported The Netherlands	Hospital admissions Reliever/rescue medication use Adverse events	Funded by GlaxoSmithKline Population indirectness – 38% participants had previously been treated with ICS
Sheffer 1996 (Sheffer et al., 1996)	**SABA+ICS** (25, 50 or 100mcg one inhalation twice per day fluticasone propionate plus SABA as needed) (three study arms combined) **SABA** (placebo inhaler twice per day plus SABA as needed) Follow-up: 12 weeks	≥12 years (range 12-72 years) with history of asthma requiring daily pharmacotherapy for ≥3 months (one week run-in period). N=307 Treatment status: not reported Asthma history: not reported Location not reported.	Reliever/rescue medication use Lung function (FEV1 and PEF)	Funded by Glaxo-Wellcome
Teper 2004 (Teper et al., 2004)	**SABA+ICS** (50 or 125 mcg fluticasone propionate, one inhalation twice per day; two study arms combined)	Infants aged < 2 years with asthmatic symptoms, family history of asthma or atopy N=34	Hospital admissions Reliever/rescue medication use	Inhalers provided by Glaxo Wellcome

Study	Intervention and comparison	Population	Outcomes	Comments
	SABA (placebo inhaler , one inhalation, twice per day) Follow-up: 6 months	Treatment status: not reported Asthma history: not reported Argentina		
Teper 2005 (Teper et al., 2005)	**SABA +ICS** (125 mcg fluticasone propionate, one inhalation twice per day, plus SABA as needed) **ICS** (placebo inhaler as one inhalation twice per day, plus SABA as needed) Follow-up: 6 months	Infants aged 6-20 months with asthmatic symptoms, family history of asthma or atopy and decreased pulmonary function. N=31 Treatment status: not reported Asthma history: not reported Argentina	Reliever/rescue medication use	Supported by GlaxoSmithKline and Trudell Medical

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence in young people/adults ≥12 years

1.1.6.1 SABA compared to ICS+SABA

Table 3: Clinical evidence summary: SABA vs ICS+SABA in young people/adults ≥12 years

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS+SABA in adults	Risk difference with SABA	Comments
Severe asthma exacerbations at >3 months (final values, lower is better)	1383 (4 RCTs) Follow-up: 12 weeks	⊕⊕⊕◯ Moderate[a]	**RR 2.87** (1.56 to 5.27)	19 per 1,000	**35 more per 1,000** (11 more to 81 more) **Clinically important benefit of ICS+SABA**	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 30 per 1000
Severe asthma exacerbations at >6 months (final values, lower is better)	2822 (3 RCTs) Follow-up: mean 43 weeks	⊕◯◯◯ Very low[b,c]	**RR 1.12** (0.87 to 1.44)	86 per 1,000	**10 more per 1,000** (11 fewer to 38 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 30 per 1000
Mortality (adverse events resulting in death, final values, lower is better)	2116 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[b,d]	**Peto OR 0.26** (0.01 to 5.86)	1 per 1,000	**0 fewer per 1,000** (0 fewer to 0 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 1 per 1000
Quality of life (Asthma quality of life questionnaire, scale range: 1-7, change scores, higher is better)	192 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[e,f,g]	-	The mean quality of life (Asthma quality of life questionnaire, scale range: 1-7, change scores, higher is better) was **1.3**	MD **0.46 lower** (0.72 lower to 0.2 lower) No clinical difference	MID=0.5 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS+SABA in adults	Risk difference with SABA	Comments
Asthma control (Asthma Control Questionnaire-5, scale range 0-6, mixed values, lower is better)	2401 (2 RCTs) Follow-up: 52 weeks	⊕⊕◯◯ Low[b]	-	The mean asthma control (Asthma Control Questionnaire-5, scale range 0-6, mixed values, lower is better) was **0.7**	MD **0.23 higher** (0.18 higher to 0.28 higher) No clinical difference	MID=0.5 (established MID)
Asthma control (Asthma control test, scale range: 5-25, change scores, higher is better)	192 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[e,f,h]	-	The mean asthma control (Asthma control test, scale range: 5-25, change scores, higher is better) was **6.2**	MD **2.2 lower** (3.26 lower to 1.14 lower) No clinical difference	MID=3 (established MID)
Reliever medication use (SABA use, puffs per day, mixed values, lower is better)	1875 (6 RCTs) Follow-up: mean 21 weeks	⊕◯◯◯ Very low[i,j,k]	-	The mean reliever medication use (SABA use, puffs per day, mixed values, lower is better) was **2.76**	MD **1.03 higher** (0.59 higher to 1.47 higher) Clinically important benefit of ICS+SABA	MID = 0.81 (established MID)
Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)	340 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[l]	-	The mean reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better) was **-1.14**	MD **0.55 higher** (0.05 higher to 1.05 higher) No clinical difference	MID= 1.05 (0.5 x final SD of both arms)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS+SABA in adults	Risk difference with SABA	Comments
Reliever/rescue medication use (night time SABA use, puffs per night, change scores, lower is better)	340 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[l,m]	-	The mean reliever/rescue medication use (night time SABA use, puffs per night, change scores, lower is better) was **-0.28**	MD **0.41 higher** (0.01 higher to 0.81 higher) No clinical difference	MID= 0.78 (0.5 x final SD of both arms)
Reliever/rescue medication use (% SABA-free nights, change scores, higher is better)	258 (1 RCT) Follow-up: 6 months	⊕◯◯◯ Very low[n,o,p]	-	The mean reliever/rescue medication use (% SABA-free nights, change scores, higher is better) was **0**	MD **14 higher** (2.91 higher to 25.09 higher) No clinical difference	MID=22.72 (0.5 x baseline SD of both arms)
Reliever/rescue medication use (% SABA-free days, change scores, higher is better)	221 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[e,q]	-	The mean reliever/rescue medication use (SABA-free days, %, change scores, higher is better) was **28.7**	MD **11.6 lower** (19.3 lower to 3.9 lower) No clinical difference	MID=14.6 (0.5 x final SD of both arms)
Lung function (% predicted FEV1, mixed values, higher is better)	2459 (3 RCTs) Follow-up: mean 10 months	⊕⊕⊕◯ Moderate[b]	-	The mean lung function (% predicted FEV1, mixed values, higher is better) was **82.45**	MD **3.47 lower** (4.35 lower to 2.59 lower) No clinical difference	MID=4.9 (0.5 x median final SDs of both arms)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS+SABA in adults	Risk difference with SABA	Comments
Lung function (FEV1, litres, change scores, higher is better)	1915 (6 RCTs) Follow-up: mean 14 weeks	⊕⊕◯◯ Low[r]	-	The mean lung function (FEV1, litres, change scores, higher is better) was **0.30** L	MD **0.17 L lower** (0.21 lower to 0.13 lower) No clinical difference	MID=0.23 (established MID
Lung function (PEF, L/min, mixed values, higher is better)	408 (9 RCTs) Follow-up: mean 18 weeks	⊕◯◯◯ Very low[i,s]	-	The mean lung function (PEF, L/min, mixed values, higher is better) was **35.4** change score	MD **18.41 change score lower** (21.54 lower to 15.27 lower) No clinical difference	MID=18.79 (established MID)
Adverse events (final values, lower is better)	5286 (8 RCTs) Follow-up: mean 22 weeks	⊕⊕⊕◯ Moderate[a]	**RR 1.00** (0.93 to 1.07)	435 per 1,000	**0 fewer per 1,000** (30 fewer to 30 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000
Pneumonia (incl RTI, final values, lower is better)	1867 (3 RCTs) Follow-up: mean 25 weeks	⊕◯◯◯ Very low[j,t]	**RD 0.01** (-0.03 to 0.05)	51 per 1,000	**10 more per 1,000** (30 fewer to 50 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS+SABA in adults	Risk difference with SABA	Comments
Inflammatory markers (FeNO, final values, lower is better)	389 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[u]	-	The mean inflammatory markers (FeNO, final values, lower is better) was **35.92** ppb	MD **12.77 ppb higher** (5.75 higher to 19.79 higher) No clinical difference	MID=22.22 (0.5 x baseline SD of both arms)

a. Downgraded by one increment because there are some concerns about risk of bias for the majority of studies (randomisation method and adherence to maintenance treatment not monitored)

b. Downgraded by two increments because the majority of evidence at high risk of bias [unclear method of randomisation and allocation concealment; no information on handling of switching groups, including how handled in analysis (switching likely due to clinician being able to add ICS to SABA treatment arm if exacerbations occurred)]

c. Downgraded by one increment for imprecision because the 95%CI crosses one MID (0.8 to 1.25)

d. Downgraded by two increments for imprecision because the 95%CI crosses both MIDs (0.8 to 1.25)

e. Downgraded by two increments because the study was at high risk of bias (14% missing outcome data, 7% difference between dropout rates per study arm and reasons for discontinuation that could have been related to participant's health status)

f. Downgraded by one increment for population indirectness (participants could have been treated with SABA, LTRAs or a combination prior to screening)

g. Downgraded by one increment for imprecision because the 95%CI crosses one MID (published MID=0.5)

h. Downgraded by one increment for imprecision because the 95%CI crosses one MID (published MID=3)

i. Downgraded by two increments because the majority of evidence is at high risk of bias (randomisation method not reported, adherence to regular treatment not monitored, high dropout rates, considerable difference in dropout rates between arms and reasons for discontinuation related to participant's health status)

j. Downgraded by one increment because of unexplained heterogeneity (I squared>70%)

k. Downgraded by one increment for imprecision because the 95%CI crosses one MID (published MID=0.81)

l. Downgraded by two increments because the study is at high risk of bias (22% missing outcome data with no information on dropout rates per study arm and reasons for discontinuation potentially related to participant's health status).

m. Downgraded by one increment for imprecision because the 95%CI crosses one MID (calculated as final SD/2=0.78)

n. Downgraded by two increments because the study is at high risk of bias (randomisation method not reported, adherence to maintenance therapy not reported, 20% dropout rate with reasons for discontinuation potentially related to participant's health status)

o. Downgrade by one increment for population indirectness (participants could have been receiving intranasal corticosteroids or intranasal cromolyn sodium at screening and were allowed to maintain this treatment at a constant dose)

p. Downgraded by one increment for imprecision because 95%CI crosses MID (calculated as final SD of both arms/2=22.72)

q. Downgraded by one increment for imprecision because the 95%CI crosses one MID (calculated as final SD of both arms/2=14.6)

r. Downgraded by two increments because the majority of evidence is at high risk of bias (randomisation method and adherence to maintenance therapy not reported, missing data and high dropout rate with reasons for discontinuation related to participant's health status)

s. Downgraded by one increment for imprecision because the confidence interval crosses one MID (published MID=18.79)

t. Downgraded by one increment for imprecision due to zero events and small sample size.

u. Downgraded by one increment because of some concerns about risk of bias due to missing outcome data.

1.1.6.2 SABA compared to ICS/LABA Combination Inhaler

Table 4: Clinical evidence summary: SABA vs ICS/LABA Combination Inhaler in young people and adults ≥12 years

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS Combination Inhaler	Risk difference with SABA	
Severe asthma exacerbations at >6 months (final values, lower is better)	2532 (2 RCTs) follow-up: 52 weeks	⊕◯◯◯ Very low[a,b]	**RR 1.61** (1.19 to 2.17)	60 per 1,000	**36 more per 1,000** (11 more to 70 more) Clinically important benefit of ICS combination	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 30 per 1000
Mortality (adverse events resulting in death, final values, lower is better)	2089 (1 RCT) follow-up: 52 weeks	⊕◯◯◯ Very low[a, b]	**Peto OR 0.25** (0.00 to 20.94)	1 per 1,000	**1 fewer per 1,000** (1 fewer to 14 more) **Clinically important difference**	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 1 per 1000
Asthma control (Asthma Control Questionnaire -5, scale 0-6, mixed values, lower is better)	2403 (2 RCTs) follow-up: 52 weeks	⊕⊕◯◯ Low[a]	-	The mean asthma control was **0.8**	MD **0.15 higher** (0.1 higher to 0.21 higher) No clinical difference	MID = 0.5 (established MID)
Reliever medication use (number of beta-2-agonist-containing actuations per day, final values, lower is better)	443 (1 RCT) follow-up: 52 weeks	⊕⊕⊕⊕ High	-	The mean number of beta-2-agonist-containing actuations per day was **0.53**	MD **0.48 higher** (0.26 higher to 0.7 higher) No clinical difference	MID = 0.81 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS Combination Inhaler	Risk difference with SABA	
Lung function (% predicted FEV1, mixed values, higher is better)	2412 (2 RCTs) follow-up: 52 weeks	⊕⊕◯◯ Low[a]	-	The mean % predicted FEV1 was **91.4**	MD **2.39 lower** (3.28 lower to 1.5 lower) No clinical difference	MID = 6.95 (0.5 x follow-up median SD of both arms)
Adverse events (final values, lower is better)	2089 (1 RCT) follow-up: 52 weeks	⊕⊕◯◯ Low[a]	**RR 1.07** (0.95 to 1.20)	392 per 1,000	**27 more per 1,000** (20 fewer to 78 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000
Inflammatory markers (FeNO, final values, lower is better)	387 (1 RCT) follow-up: 52 weeks	⊕⊕◯◯ Low[b, c]	-	The mean FeNO was **37.65**	MD **11.04 higher** (3.82 higher to 18.26 higher) No clinical difference	MID = 18.09 (0.5 x final SD of both arms)

a. Downgraded by 2 increments due to bias arising from the randomisation process and deviations from the intended interventions

b. Downgraded by 1 increment if the confidence intervals crossed one MID and 2 increments if the confidence intervals crossed both MIDs

c. Downgraded by 1 increment due to bias arising from missing outcome data

1.1.6.2 ICS+SABA compared to ICS/LABA Combination Inhaler as needed

Table 5: Clinical evidence summary: ICS+SABA vs ICS/LABA Combination Inhaler as needed in adults

Outcomes	№ of 23uestion23as (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS Combination Inhaler	Risk difference with ICS+SABA	
Severe asthma exacerbations at > 6 months (final values, lower is better)	3520 (2 RCTs) follow-up: 52 weeks	⊕◯◯◯ Very low[a, b]	**RR 1.42** (1.11 to 1.80)	60 per 1,000	**25 more per 1,000** (7 more to 48 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 30 per 1000
Mortality (adverse events resulting in death, final values, lower is better)	3075 (1 RCT) follow-up: 52 weeks	⊕◯◯◯ Very low[a, b,]	**RR 1.97** (0.18 to 21.65)	1 per 1,000	**1 more per 1,000** (1 fewer to 14 more) **Clinically important difference**	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 1 per 1000
Asthma control (Asthma Control Questionnaire-5, scale range 0-6, mixed values, lower is better)	3286 (2 RCTs) follow-up: 52 weeks	⊕⊕◯◯ Low[b]	-	The mean asthma control was **0.8**	MD **0.07 lower** (0.11 lower to 0.04 lower) No clinical difference	MID = 0.5 (established MID)
Reliever medication use (number of beta-2-agonist-containing actuations per day, final values, lower is better)	445 (1 RCT) follow-up: 52 weeks	⊕⊕⊕⊕ High	-	The mean number of beta-2-agonist-containing actuations per day was **0.53**	MD **0.01 lower** (0.16 lower to 0.14 higher) No clinical difference	MID = 0.81 (established MID)

Outcomes	№ of 23uestion23as (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS Combination Inhaler	Risk difference with ICS+SABA	
Lung function (% predicted FEV1, mixed values, higher is better)	3343 (2 RCTs) follow-up: 52 weeks	⊕⊕◯◯ Low[b]	-	The mean % predicted FEV1 was **91.4**	MD **1.11 higher** (0.43 higher to 1.8 higher) No clinical difference	MID = 6.93 (0.5 x final SD of both arms)
Adverse events (final values, lower is better)	3075 (1 RCT) follow-up: 52 weeks	⊕⊕◯◯ Low[b]	**RR 1.09** (1.01 to 1.19)	392 per 1,000	**35 more per 1,000** (4 more to 74 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000
Inflammatory markers (FeNO, final values, lower is better)	390 (1 RCT) follow-up: 52 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean FeNO was **37.65**	MD **1.73 lower** (8.33 lower to 4.87 higher) No clinical difference	MID = 22.5 (0.5 x baseline SD of both arms)

a. Downgraded by 1 increment if confidence intervals crossed one MID and 2 increments if confidence intervals crossed both MIDs

b. Downgraded by 2 increments due to bias arising from the randomisation process and deviations from the intended interventions

c. Downgraded by 1 increment due to bias arising from missing outcome data

Summary of the effectiveness evidence in children aged 5-11 years

Table 6: Clinical evidence summary: SABA vs ICS+SABA for initial asthma management in children aged 5-11 years

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS+SABA in children	Risk difference with SABA	Comments
Severe asthma exacerbations at >3 months (final values, lower is better)	319 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,b]	**RR 1.42** (0.84 to 2.39)	132 per 1,000	**55 more per 1,000** (21 fewer to 184 more) Clinically important benefit of ICS+SABA	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 30 per 1000
Adverse events (final values, lower is better)	672 (2 RCTs) Follow-up: 12 weeks	⊕⊕⊕⊕ High	**RR 1.08** (0.97 to 1.21)	641 per 1,000	**51 more per 1,000** (19 fewer to 135 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000
Adrenal insufficiency (abnormal response to low-dose ACTH stimulation, final values, lower is better)	61 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[c,d]	**RR 6.15** (0.68 to 55.46)	24 per 1,000	**126 more per 1,000** (8 fewer to 1,328 more) Clinically important benefit of ICS+SABA	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000
Pneumonia (final values, lower is better)	319 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,d]	**OR 19.71** (0.31 to 1252.08)	0 per 1,000	**10 more per 1,000** (10 fewer to 30 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000

a. Downgraded by two increments because study at high risk of bias (randomisation method not reported and 62.5% adherence to study medications)

b. Downgraded by one increment for imprecision because the 95% CI crosses one MID (0.8-1.25)

c. Downgraded by two increments because study at high risk of bias (subgroup analysis of participants who were willing to have blood tests with complete-case analysis used; included only participants with pre and post study measurements; dropout rates in the subgroup not reported)

d. Downgraded by two increments for imprecision because the 95%CI crosses both MIDs (0.8-1.25)

Summary of the effectiveness evidence in under 5 years

Table 7: Clinical evidence summary: SABA vs ICS+SABA for initial asthma management in under 5 years

Outcomes	№ of 26uestion26as (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS+SABA in infants	Risk difference with SABA	
Hospital admissions at >6 months (final values, lower is better)	126 (2 RCTs) Follow-up: 6 months	⊕◯◯◯ Very low[a,b]	**RD 0.03** (-0.03 to 0.10)	0 per 1,000	**30 more per 1,000** (30 fewer to 100 more) Clinically important benefit for ICS + SABA	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 30 per 1000
Reliever/rescue medication use (SABA use, puffs per day, change scores, lower is better)	37 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[c,d]	-	The mean change in daily SABA use was **-0.22 puffs per day**	MD **0.34 higher** (0.2 lower to 0.88 higher) No clinical difference	MID=0.81 (established MID)
Reliever/rescue medication use (daytime SABA use, puffs per day, mixed values, lower is better)	253 (2 RCTs) Mean follow-up: 19 weeks	⊕◯◯◯ Very low[e,f,g]	-	The mean change in daytime SABA use was **0.37 puffs per day**	MD **0.07 higher** (0.13 lower to 0.27 higher) No clinical difference	MID=0.30 [0.5 x SD (final values only) at follow-up of both arms)]
Reliever/rescue medication use (night time SABA use, puffs per night, mixed values, lower is better)	253 (2 RCTs) Mean follow-up: 19 weeks	⊕⊕⊕◯ Moderate[e]	-	The mean change in nighttime SABA use was **0.11 puffs per night**	MD **0.01 lower** (0.07 lower to 0.05 higher) No clinical difference	MID=0.11 (0.5 x SD (final values only) at follow-up of both arms)

Outcomes	№ of 26uestion26as (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS+SABA in infants	Risk difference with SABA	
Reliever/rescue medication use (days with SABA use, final values, lower is better)	56 (2 RCTs) Follow-up: 6 months	⊕◯◯◯ Very low[h,i]	-	The mean number of days with SABA use, was **8.2**	MD **12.61 higher** (4.05 higher to 21.18 higher) Clinically important benefit of ICS+SABA	MID=2.23 (0.5 x follow-up median SD of both arms)
Adverse events (final values, lower is better)	96 (1 RCT) Follow-up: 6 months	⊕◯◯◯ Very low[a,j]	**RR 0.97** (0.70 to 1.33)	625 per 1,000	**19 fewer per 1,000** (188 fewer to 206 more) No clinical difference	MID (imprecision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000

a. Downgraded by one increment for population indirectness (38% participants had previously been treated with ICS)

b. Downgraded by two increments due to inadequate sample size (optimal information size calculator power = 56%)

c. Downgraded by two increments because the study is at high risk of bias (adherence to regular treatment not monitored and 29% dropout rate with reasons potentially related to participant's health status)

d. Downgraded by one increment for imprecision because 95%CI crosses one MID (published MID=0.81)

e. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

f. Downgraded by one increment due to moderate heterogeneity that was not explained (I^2=51%)

g. Downgraded by one increment due to the 95%CI overlapping one MID (calculated as mean follow-up SD/2 = 0.26)

h. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence to treatment not monitored), missing outcome data (12% missing with complete case analysis, and reasons for discontinuation related to participant's health status)

i. Downgraded by one increment due to unexplained heterogeneity (I^2 =88%)

j. Downgraded by two increments for imprecision because 95%CI crosses both MIDs (0.8-1.25)

Table 8: Clinical evidence summary: SABA vs ICS/SABA combination inhaler as needed for initial asthma management in under 5 years

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS combination	Risk difference with SABA	
Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)	159 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[a,b]	-	The mean change in daytime SABA use was **-0.17 puffs per day**	MD **0.08 higher** (0.05 lower to 0.21 higher) No clinical difference	MID=0.2 (0.5 x final SD of both arms)
Reliever/rescue medication use (night time SABA use, puffs per night, change scores, lower is better)	159 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[a,c]	-	The mean change in nighttime SABA use was **-0.12 puffs per night**	MD **0.04 higher** (0.04 lower to 0.12 higher) No clinical difference	MID=0.11 (0.5 x final SD of both arms)

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

b. Downgraded by one increment due to the 95%CI overlapping one MID (calculated as mean follow-up SD/2 = 0.2)

c. Downgraded by one increment due to the 95%CI overlapping one MID (calculated as mean follow-up SD/2 = 0.11)

Table 9: Clinical evidence summary: SABA+ICS vs ICS/SABA combination inhaler as needed for initial asthma management in under 5 years

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS combination	Risk difference with SABA+ICS	
Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)	214 (1 RCT) Follow-up: 12 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in daytime SABA use was **-0.17 puffs per day**	MD **0.07 lower** (0.18 lower to 0.04 higher) No clinical difference	MID= 0.21 (0.5 x final SD of both arms)
Reliever/rescue medication use (night time SABA use, puffs per night, change scores, lower is better)	214 (1 RCT) Follow-up: 12 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in nighttime SABA use, was **-0.12 puffs per night**	MD **0.02 higher** (0.03 lower to 0.07 higher) No clinical difference	MID= 0.10 (0.5 x final SD of both arms)

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study with the relevant comparison was included in this review(FitzGerald, et al., 2020). This is summarised in the health economic evidence profile below **Table 10** and the health economic evidence table in Appendix H.

1.1.7.2 Excluded studies

Five economic studies relating to this review question were identified but were excluded due to limited applicability(Briggs, et al., 2006),(Doull, et al., 2007, Miyagawa, et al., 2006) or selectively excluded due to the availability of more applicable evidence(Buendia, et al., 2021, Sadatsafavi, et al., 2021). These are listed in Appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 10: Health economic evidence profile: Maintenance ICS plus as-needed SABA vs as-needed combination inhaler ICS/formoterol in people with asthma aged 12 and over

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
FitzGerald 2020(FitzGerald et al., 2020) (UK)	Partially applicable[a]	Potentially serious limitations[b]	• Markov model with transition probabilities based on SYGMA 2 RCT analysis (Bateman, et al., 2018). • Cost-utility analysis • Population: Asthma patients aged ≥ 12 years with asthma uncontrolled on as-needed SABA or controlled on regular low-dose ICS or LTRA plus as-needed SABA • Comparators: 1. Maintenance ICS plus as-needed SABA 2. As-needed combination inhaler ICS/formoterol • Time horizon: Lifetime	2-1: saves £293[c]	2-1: 0.001	As-needed combination inhaler ICS/ formoterol is dominant (greater QALY gain at a lower cost)	Several one-way and scenario analyses were conducted. The results were found to be sensitive to the following variables: annual exacerbation rates; mean number of inhalation of ICS/formoterol and ICS per day; discount rates. In all sensitivity analyses, except for changes in annual exacerbation rates, ICS/formoterol dominates ICS plus SABA.

Abbreviations: BNF= British national formulary; ED= emergency department; EQ-5D-5L= EuroQoL–5 Dimension; ICER= incremental cost-effectiveness ratio; ICS= inhaled corticosteroids; n/a= not available; LABA= long-acting β2-antagonist; LTRA = leukotriene receptor antagonists; MIMS= monthly index of medical specialties; PSSRU= personal Social Services Research Unit; QALY= quality-adjusted life years; RCT= randomised controlled trial; SABA= short-acting β2-antagonist.

(a) SYGMA 2 population including 54% of people who were not treatment-naïve

(b) The analysis was based on SYGMA 2 which included both people who were treatment-naïve and people who were receiving ICS before the enrolment. The clinical review included a post-hoc subgroup analysis on treatment-naïve people from SYGMA 2 in line with the protocol, finding greater benefits on this subgroup. Hence, this analysis is likely

underestimating the benefits of combination inhaler on a treatment-naïve population. Some relevant outcomes, such as asthma control and non-severe exacerbations were not included. These were found to be similar in previous study although SYGMA 2 found non-clinically significant benefits in asthma control and quality of life with ICS plus SABA compared to combination ICS/formoterol inhaler. QALYs were calculated using EQ-5D-5L instead of EQ-5D-3L.

(c) 2018 UK pounds. Cost components included: Inhalers, system steroids, inpatient hospitalisation, ED, ambulance, GP visit.

1.1.9 Economic model

This area was not prioritised for health economic modelling, however a cost comparison was undertaken.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 11: Unit costs per class

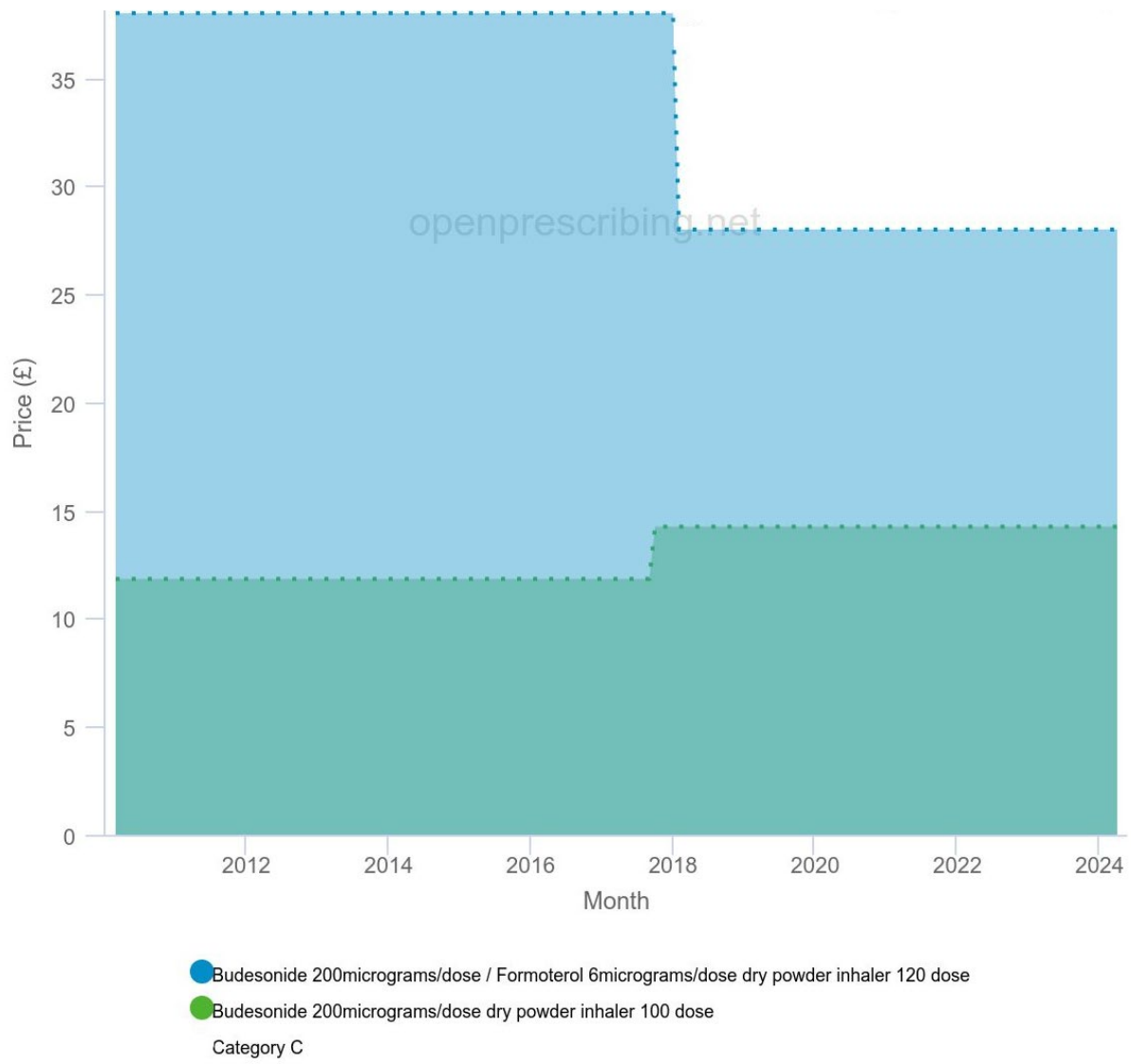
Class	Drug[a]	Cost per 100µg	Dose per day	Cost per day (drug)	Cost per day (class)[e]
ICS	Budesonide	£0.07	300 µg[c]	£0.21	£0.15
	Beclometasone	£0.04	350 µg[c]	£0.13	
	Ciclesonide	£0.34	120 µg[c]	£0.41	
	Fluticasone	£0.13	175 µg[c]	£0.23	
	Mometasone	£0.17	200 µg[c]	£0.34	
SABA	Salbutamol	£0.001	100 – 200 µg up to 4 times a day	£0.1 - £0.8	£0.011[d]
	Terbutaline	£0.0138	500 µg up to 4 times a day	£0.07 - £0.28	
ICS/LABA	Budesonide with formoterol	£0.12[b]	1 - 6 puffs as required	£0.12 – £0.72	£0.12 – £0.72

(a) Formulations included: pressurised inhalation and inhalation powder (including refill and autohaler)
(b) Per 100 µg of Budesonide
(c) Midpoint low ICS dose from NICE NG80 guideline
(d) Calculated assuming minimum dose reported in the BNF
(e) Calculated as a weighted average using distribution of drug usage
Source: BNF for dosage and cost per item,(Joint Formulary Committee, 2024) PCA for weighted average price across all the formulations and cost of drug class.(Health and Social Care Information Centre, 2014)

It is worth noting that, since 2018, the price of Budesonide has increased whereas the price of the combination inhaler, Budesonide and Formoterol, has dropped more than 25%, significantly reducing their difference in price. This is particularly evident from **Figure 1** where the difference in price at each year is represented by the green area.

The information from Table 11 and **Figure 1** suggest that it is possible for a therapy with ICS/formoterol to be less expensive than an ICS therapy, particularly if the first is offered as a reliever and the latter as a maintenance therapy. The recent reduction of the price difference between these two drugs prompted us to carry out a cost analysis on the resource use of the studies included in the clinical review: Beasley 2019(Beasley et al., 2019) and the post-hoc analysis on SYGMA 1 and SYGMA 2(Bateman et al., 2021). The cost-comparison analysis is presented in section 1.1.10.1 Cost-comparison analysis.

Figure 1: Comparison of price between price of Budesonide and Budesonide with Formoterol over time in England



Source: OpenPrescribing (Bennett Institute of Applied Data, 2022)

1.1.10.1 Cost-comparison analysis

A cost-comparison analysis was conducted using UK unit costs and resource use reported in the three trials included in the clinical review: Beasley 2019(Beasley et al., 2019), SYGMA 1 and SYGMA 2(Bateman et al., 2021). In line with the clinical review, only outcomes of people who were treatment-naïve at the time of recruitment were extracted from SYGMA 1 and SYGMA 2.

In Beasley 2019 and SYGMA 1, three strategies were compared:

1. SABA as needed
2. Low-dose ICS (maintenance) + SABA as needed
3. Low-dose combination inhaler (ICS + formoterol) as needed

In SYGMA 2, SABA as needed was not included, so only the comparator ICS plus SABA and combination inhaler were compared.

Unit costs were collected from BNF and PCA was used to calculate the average cost per µg across all the formulations. These are presented in Table 12.

Table 12: Unit costs used in the cost-comparison analysis

Class	Drug	Cost per 100 µg/inhalation
ICS	Budesonide	£0.07 per 100 µg
SABA	Salbutamol	£0.01 per 100 µg
	Terbutaline	£0.0138 per 100 µg
ICS/LABA	Budesonide with formoterol	£0.12 per 100 µg[(a)]

Source: BNF for cost per mg,(Joint Formulary Committee, 2024) PCA for weighted average price across all the formulations(Health and Social Care Information Centre, 2014)

a) Per 100 µg of Budesonide

Daily dosage of drugs assumed in each arms of the trials are presented in Table 13. Noticeably, the two SYGMA trials did not report the dosage of SABA used and therefore it is impossible to calculate the cost of SABA as needed therapy or of the SABA component in the ICS + SABA strategy. As SABA is relatively cheap, these costs are not expected to be particularly relevant although this implication will be discussed further.

Table 13: Resource use and cost in each trial per patient

	SABA	ICS + SABA as needed	Combination ICS/formoterol as needed
Beasley 2019			
Daily Budesonide dose (µg)	0	222 (207 – 237)	107 (93 – 121)
Daily SABA dose (µg)	101 (80 – 111)	52 (38 – 66)	0
SYGMA 1			
Daily Budesonide dose (µg)	0	335 (261 – 382)	70 (18 – 162)
Daily SABA dose (µg)	NR	NR	NR
SYGMA 2			
Daily Budesonide dose (µg)	NA	251 (151 – 332)	73 (21 – 177)
Daily SABA dose (µg)	NA	NR	NR

Abbreviations: NA: not available; NR: not reported.

Table 14 illustrates the cost of each strategy with the 95% confidence intervals between bracket in the three trials.

Table 14: Annual pharmaceutical cost per patient

Trial	SABA	ICS + SABA as needed	Combination ICS/formoterol as needed
Beasley 2019	£4 (£3 to £4)	£60 (£55 to £64)	£46 (£39 to £52)
SYGMA 1	NR	£87[(a)] (£68 to £99)	£30 (£8 to £69)
SYGMA 2	N/A	£65[(a)] (£39 to £86)	£31 (£9 to £75)

Abbreviations: N/A: not available; NR: not reported.
(a) Not including the cost of SABA

In all trials, the cost of the combination inhaler therapy is lower than ICS + SABA as needed therapy, although the confidence intervals overlap in SYGMA 1 and SYGMA 2. However, the resource use of as-needed SABA could not be extracted from the subgroup analysis on the two SYGMA trials, hence the cost of ICS + SABA in SYGMA 1 and SYGMA 2 is an

underestimation. These results are in line with FitzGerald 2020(FitzGerald et al., 2020), which found a lower pharmaceutical cost with as-needed combination inhaler strategy compared to maintenance ICS and SABA strategy. As the clinical review found benefits, although not clinically significant, of combination inhaler over ICS + SABA in terms of severe exacerbations, it is possible that ICS/formoterol dominates the latter (less costly and more effective), especially if less severe exacerbations are expected to improve quality of life and reduce costs. Interestingly, using prices before the reduction of 2018, as shown in **Figure 1**, would have resulted in ICS plus SABA being cheaper than combination inhaler, suggesting that the cost advantage of the combination inhaler is relatively recent.

Although SABA is, by far, the cheapest strategy, as shown by the calculation on Beasley 2019 trial, it is also associated with the poorest clinical outcomes and, therefore, its cost-effectiveness is doubtful.

1.1.11 Evidence statements

Economic

- One cost–utility analysis found that as needed combination inhaler ICS/formoterol was dominant (greater QALY gain at lower cost) compared to maintenance ICS plus as needed SABA for treating uncontrolled asthma in people over 12 years. This analysis was assessed as partially applicable with potentially serious limitations.

1.2. The committee's discussion and interpretation of the evidence

The committee discussion on studies in children under age 5 identified in review Q (drug combinations and sequencing for asthma management) is covered in this CDE. This is because it was advantageous to discuss all evidence in children aged under 5 years together to inform recommendations.

1.2.1. The outcomes that matter most

The purpose of asthma medication is to relieve symptoms, improve quality of life and prevent exacerbations, acute attacks and asthma deaths. The occurrence of severe asthma exacerbations is of major importance as these are associated with an increased risk of death and have a significant deleterious effect on quality of life. The outcomes considered for this review were severe asthma exacerbations, mortality, quality of life, asthma control, hospital admissions, reliever/rescue medication use, lung function, adverse events and inflammatory markers. For purposes of decision making, all outcomes were considered equally important and were rated as critical by the committee.

The protocol specified that severe asthma exacerbations should be reported at ≥6 months. However, many RCTs identified had a follow-up of 12 weeks, so the outcome severe asthma exacerbations was reported as ≥3 months and ≥6 months separately. Studies reported reliever/rescue medication use in a variety of ways, including as a puffs per day, days with SABA use, nighttime or daytime SABA use or SABA-free days. As an established MID is published for puffs per day, reliever/rescue medication use expressed in this way was preferable.

No evidence was identified for the outcomes of linear growth or bone mineral density.

1.2.2 The quality of the evidence

Adults and young people aged ≥12 years

Thirteen RCTs were conducted in adults and young people aged 12 years or over. All these studies compared SABA (as needed) alone with regular ICS plus SABA (as needed). Two of these studies also investigated a third arm comprising an ICS/formoterol combination inhaler used as required.

Overall, the evidence from these studies ranged from very low to high quality, with many findings showing very low or low certainty in GRADE. Findings were often downgraded in GRADE due to concerns about risk of bias (for example, unclear randomisation or allocation concealment method, adherence to treatment not considered, missing data and reasons for discontinuation that could have been related to participant's health status) or imprecision (wide confidence intervals). For a small number of outcomes there were some concerns about unexplained heterogeneity or population indirectness.

Children aged 5 to 11 years

Two RCTs were conducted in children aged 5 to 11 years. Both compared SABA (as needed) alone with regular ICS plus SABA (as needed). The quality of evidence was very low for all outcomes, except for one (adverse events). Downgrading in GRADE was due to high risk of bias (unclear randomisation method, low adherence to treatments) and imprecision. Of note, the finding on adrenal insufficiency was downgraded by two increments because the relevant study was at high risk of bias because it was based on a subgroup analysis of participants who were willing to have blood tests and dropout rates in the subgroup were not reported.

No evidence was identified that compared any ICS combination inhaler (as needed) with either SABA (as needed) alone or ICS plus SABA (as needed).

Children aged under 5 years

Five RCTs were conducted in children under age 5 years. These all compared SABA (as needed) alone with regular ICS plus SABA (as needed). One study included an additional trial arm providing an ICS combination inhaler (ICS/SABA taken as needed), so this single study provided evidence for SABA (as needed) compared to ICS/SABA combination inhaler (as needed) and both of these compared to regular ICS plus SABA as needed. . Overall, the five studies provided evidence that was very low to moderate quality. Evidence was downgraded due to concerns about risk of bias (for example randomisation method unclear, missing outcome data and or adherence to treatment not considered), imprecision, unexplained heterogeneity and, in one case, population indirectness.

To inform a single discussion on recommendations for children under 5 years, evidence from studies on this age group was also presented from review 3.2 on drug combinations and sequencing for asthma management. Two RCTs (one of which was a cross-over study) were presented, with very low/low quality of evidence. One considered regular ICS versus regular montelukast and a third arm using an ICS/SABA combination inhaler as needed; the second study compared regular ICS to regular montelukast. These two studies were downgraded for quality due to risk of bias (randomisation process, deviations from the intended interventions and missing outcome data) and imprecision.

Neither review on children under 5 years, included any evidence that compared regular ICS or an ICS combination inhaler with or without the addition of an LTRA.

1.2.3 Benefits and harms

Adults and young people aged ≥12 years

SABA as needed versus regular ICS plus SABA as needed

For the comparison of SABA as needed versus regular ICS plus SABA as needed, clinically important benefits for ICS plus SABA were reported for severe asthma exacerbations at >3 months (35 exacerbations fewer out of a 1000) and reliever/rescue medication use (a mean difference of 1.03 fewer SABA puffs per day). Findings for other outcomes, did not indicate a clinically important benefit for either arm.

SABA as needed versus ICS/formoterol combination inhaler as needed

For this comparison, a clinically important benefit of 36 fewer severe asthma exacerbations per 1000 at ≥6 months, was noted for ICS/formoterol combination inhaler. Findings for other outcomes, did not indicate a clinically important benefit for either arm.

Regular ICS plus SABA as needed versus ICS/formoterol combination inhaler as needed

Findings for this outcome did not reach clinically important benefits for either arm using the committee's agreed MIDs. However, it was noted that the outcome severe asthma exacerbations at ≥6 months was close to a clinically important benefit for ICS/formoterol combination inhaler, as 25 fewer exacerbations per 1000 were reported for this arm (agreed MID is 30/1000). Findings for other outcomes, did not indicate a clinically important benefit for either arm.

The committee concluded that data on severe exacerbations favoured using ICS/LABA combination inhalers over the two other treatment options.

Children aged 5 to 11 years

SABA as needed versus ICS plus SABA as needed

For this comparison there was a clinically important benefit of ICS plus SABA, with 55 per 1000 fewer severe asthma exacerbations at >3 months, compared to SABA. Although contrary to committee expectations, there was also a clinically important benefit for ICS plus SABA for the outcome adrenal insufficiency. The committee discussed the possibility that this might be a result of intermittent oral corticosteroid use to treat the larger number of exacerbations experienced in the SABA only group. Findings for other outcomes, did not indicate a clinically important benefit for either arm.

Children aged under 5 years

SABA as needed versus ICS plus SABA as needed

A clinically important benefit for ICS plus SABA as needed was identified for hospital admissions (30 fewer per 1000) and reliever/rescue medication use (a mean difference of 12.61 fewer days with SABA use). Findings for other outcomes, did not indicate a clinically important benefit for either arm.

SABA as needed versus ICS/SABA combination inhaler as needed, and ICS plus SABA as needed versus ICS/SABA combination inhaler as needed.

No clinically important benefits were identified for any outcome

1.2.4 Cost effectiveness and resource use

Six health economics studies were identified for this review. Three were excluded for looking at a combination inhaler ICS/LABA different than ICS/formoterol. The remaining three studies were based on the same trials: SYGMA 1 and SYGMA 2 (age ≥ 12). One was an UK cost-utility analysis whereas the other two were conducted in other settings, Canada and Colombia. Hence, these latter two were selectively excluded and only the UK study, FitzGerald, was presented to the committee.

This was a cost-utility analysis based on SYGMA 2 randomised controlled trial looking at maintenance ICS plus SABA as needed therapy compared to ICS/formoterol combination inhaler as needed. Although the analysis had a UK NHS perspective, SYGMA 2 population included 50% of people who were taking ICS before the enrolment and, as such, were outside the protocol. People who are treatment-naïve are expected to benefit more from ICS/formoterol therapy, as demonstrated by Bateman 2021 post-hoc analysis on the two SYGMA trials included in the clinical review, so SIGMA 2 might underestimate the effectiveness of the combination inhaler. For this reason, the analysis was assessed as partially applicable and with potentially serious limitation. The study found that ICS/formoterol combination inhaler dominates maintenance ICS plus PRN SABA, being cheaper and, at the same time, more effective. Savings of ICS/formoterol therapy were mostly attributed to the reduced pharmaceutical cost.

Unit costs were presented to the committee for people aged 12 or above. Data from Open Prescribing showed that the difference in cost between ICS/formoterol and ICS has dropped recently, following a reduction in price of ICS/formoterol and a slight increase in price of ICS in 2018. Yet, ICS/formoterol remained more expensive than ICS or SABA alone, so the hypothesis that a therapy with ICS/formoterol is cheaper than ICS plus SABA was tested in a bespoke cost-comparison analysis which used data from the trials included in the clinical review and relevant UK sources. In a paediatric population (≤12), ICS maintenance dosages are typically half those recommended in the over 12s, so the anticipated cost of ICS therapy is expected to be halved in this age group.

BNF and PCA were used to calculate the cost per 100 µg of budesonide (ICS), salbutamol (SABA) and budesonide with formoterol (ICS/LABA). The first source was used for unit costs, whereas the latter was used to calculate a weighted average cost across all formulations. Daily pharmaceutical consumption data in the three strategy arms were collected from the two studies included in the clinical review: Beasley 2019 and Bateman 2021. The first was an open-label trial enrolling adults whereas the latter was a post-hoc analysis on treatment-naïve people ≥12 enrolled in the two SYGMA trials. Daily dosage data showed a higher ICS consumption in the ICS plus SABA group. By contrast, utilisation of ICS/formoterol was fairly low, with around one inhalation every two days in Beasley 2019, and around one every three days in the SYGMA trials. The total pharmaceutical cost was found to be higher in the ICS plus SABA group. The difference was statistically significant in Beasley 2019, but not significant in the two SYGMA trials, although the estimation of the pharmaceutical cost of ICS plus SABA in these latter trials did not include the SABA component. SABA alone was, by far, the cheapest strategy, with an expected cost of only £3 per year.

The committee members were aware that, in some cases, inhalers used PRN may exceed their shelf life before having exhausted all the doses. This may represent a significant waste of resource. The electronic Medicines Compendium (eMC) reports a shelf life of 3 months after first opening an MDI (metered dose inhaler) ICS/LABA and 3 years shelf life for DPI (dry powder inhaler) ICS/LABA , although the committee acknowledged that people are usually advised not to use the inhaler 6 months after opening. The prescription cost analysis showed that ICS/formoterol is predominantly prescribed as DPI. For instance, the most common formulation of Budesonide/formoterol , Symbicort 200/6, is prescribed as DPI in 94% of cases and as MDI only in 4%. This implies that the shelf life after first opening should be long enough not to cause any significant waste. Assuming two inhalers needed per year, as per prescriber's advice, ICS/formoterol therapy would still be cost-saving. In contrast, ICS and SABA are frequently prescribed in MDI form, increasing the likelihood of significant wastage or inefficiency if they expire before all doses are used up, which is expected to occur more often compared to DPI ICS/formoterol inhalers.

The committee discussed the clinical evidence in light of the economic evidence provided. Despite not achieving clinical importance, ICS/formoterol was found to reduce the numbers of severe exacerbations: 36 fewer per 1,000 compared to SABA alone, 25 fewer per 1,000 compared to ICS plus SABA. These clinical benefits combined with potential healthcare

savings showed by the cost-analysis and the included health economic study, suggest that ICS/formoterol dominates ICS plus SABA (both cheaper and more effective). The committee were aware that most people who were taking ICS/formoterol in the UK, were also taking SABA as a reliever, as ICS/LABA is currently licensed as a maintenance therapy in the UK. Although the evidence showed that SABA alongside ICS/formoterol is not needed, the additional cost of SABA is expected to be very low and unlikely to change overall cost-effectiveness conclusions.

The committee agreed that SABA alone should not be offered to people with asthma. Despite being the cheapest therapy, SABA alone was associated with the poorest clinical outcomes, including severe exacerbations, poor lung function and asthma control. Moreover, the committee agreed that excessive doses of SABA can be associated with exacerbation and mortality in the long-term. The committee acknowledged that many people in the UK are treated with SABA alone and, therefore, additional resources would be needed initially to switch them to a combination therapy. However, concerns were raised that a significant proportion of people on a SABA alone might not actually have asthma. This implies that some of those taking SABA alone would not need to switch to an ICS-based therapy if their diagnosis is not confirmed by the recommended diagnostic pathway (see evidence review 1.11).

The committee discussed the benefits of combination inhaler compared to maintenance ICS plus as-needed SABA. Overall, the committee agreed that the health economic and clinical evidence shows superiority of the first with respect to the latter, but concerns were raised on whether the evidence could be extrapolated to a paediatric population as no study on children was identified. Therefore they recommend ICS/formoterol only for those aged 12 or over. This represents an important change from current practice, which is ICS plus SABA. Although combination inhalers are generally more expensive, the cost analysis and the included economic and clinical evidence showed that, in the long-term, an ICS/formoterol strategy reduces costs and increases health outcomes. Therefore, this recommendation is expected to enhance the efficiency of the NHS.

Data from the Prescription Cost Analysis (PCA) unequivocally showed that, compared to the alternative ICS and SABA, ICS/LABA combination inhalers are predominantly prescribed as DPI. Since this is not expected to change due to the recommendation, it is likely that some people who are taking ICS or SABA through an MDI inhaler will switch to a DPI ICS/formoterol. This may require initial counselling and education to adapt to the different inhalation technique, although the committee do not expect additional resources to be needed as counselling should be included in the review consultation as per best practice when prescribing an inhaler.

There was no evidence for ICS/formoterol in the paediatric population. Clinical evidence showed that ICS plus SABA as needed was superior to SABA alone, so the committee make a recommendation for low-dose ICS plus SABA. This reflects current practice and so will not require additional NHS resources.

1.2.5 Other factors the committee took into account

Environmental impact of inhalers

The committee noted that ICS/LABA for PRN use is predominantly prescribed as a dry powder inhaler (DPI) whereas SABA and ICS are often prescribed as metered dose inhalers (MDI). This is particularly true for SABA as, for instance, only 3% of salbutamol is sold as DPI according to the most recent Prescription Cost Analysis (PCA) database. By contrast, 96% of budesonide/formoterol 200/6, the only ICS/formoterol currently licensed for AIR therapy in the UK, is prescribed as DPI. There is an ongoing discussion on the environmental benefits of DPIs over MDIs, since the latter contain hydrofluorocarbons (HFCs), which are potent greenhouse gases(Janson, et al., 2020). Hence, if usage of ICS/formoterol (mostly DPI) increases while that of ICS (both DPI and MDI) and SABA (predominantly MDI)

decreases, significant benefits to the environment specifically in terms of lower greenhouse gases produced may occur. This, in turns, could lead to indirect benefits to health due to a lower incidence of noncommunicable diseases caused by climate change.

The committee also noted that some people with asthma would still need to have an MDI SABA available to use via a spacer in the event of a severe asthma attack. These are almost all children, some of whom find it difficult to use a DPI during an attack.

Use of SABA alone

Retrospective surveys, notably the NRAD survey in the UK, have shown that use of SABA alone is disproportionately linked to deaths from asthma (Attar-Zadeh, et al., 2021). Taken together with the inferiority of SABA only therapy demonstrated in the studies presented to the committee, it was felt that a recommendation should be made advising against the use of SABA without concomitant use of an ICS. The committee were also aware of other studies which did not match our inclusion criteria exactly, but which approximate to them reasonably closely (Haahtela, START study). These all suggest that it is beneficial to treat confirmed asthma with ICS from the onset rather than rely on SABA alone and are therefore supportive of this recommendation.

ICS/formoterol combination inhalers

The superiority of ICS combination inhalers compared to SABA alone is consistent with the committee's knowledge and experience. There may be a very small number of people with very mild asthma who will never have a significant asthma exacerbation despite not being given inhaled steroids, but it is not possible to reliably predict who these people are at presentation, and treating with inhaled steroids greatly reduces the risks of future exacerbations. It was considered that the use of ICS combination inhalers as needed provides the ability to greatly increase the ICS dose for a day or two, and thereby prevents the need for oral steroids during a severe exacerbation. Pathophysiological considerations would also support the idea of using treatment which reduces airway inflammation in asthma, which SABA alone will not do.

Poor adherence is an important issue in asthma management; using ICS combination inhalers as required mitigates this problem by providing some ICS without the need for daily (usually twice daily) treatment.

Factors relevant for children under 5 years

The evidence in children under 5 years was considered limited, though it did lend some support to the use of ICS in addition to SABA as initial therapy. There was insufficient evidence to assess the relative value of ICS provided as a daily maintenance therapy, or in the form of an ICS combination inhaler to be used as needed. Accordingly, the committee considered research recommendations to be valuable to address this gap.

The committee considered the recommendations made by consensus for the NICE guideline NG80 (Asthma: diagnosis, monitoring and chronic asthma management) in formulating recommendations, and discussed amendments to these taking into account the limited evidence, their clinical experience and the well-known difficulties in diagnosing asthma in children under 5 years. The committee wanted to avoid implying that SABA alone is an appropriate therapy for children under 5 years (see above). SABA is therefore recommended as a reliever, in addition to a trial of ICS as maintenance therapy. The use of a trial of ICS is consistent with the NG80 guidelines but has been refined to give greater clarity on situations in which the trial should be considered, and how improvement in, or continuation of,

symptoms should be assessed at appropriate time points afterwards. Special note was made of situations where a child has an acute episode requiring systemic steroids and/or hospitalisation; the committee's clinical experience, and audit data, suggest that such children should be strongly suspected of having asthma (especially if have a family history or atopy).

In line with consensus recommendations made in NG80, the committee agreed that the option to consider an LTRA as an additional therapy in addition to the ICS if the child remains uncontrolled, remained appropriate. Likewise, the committee considered the recommendation in NG80 to refer to a child who remains uncontrolled to a specialist in asthma for further investigation and management, remains appropriate.

1.2.5 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.3, 1.7.1, 1.8.1, 1.9.1, 1.9.2, 1.9.3, 1.9.4, 1.9.5 and 1.9.6 and the research recommendation on the use of ICS/formoterol as needed as the initial treatment for newly diagnosed asthma in children aged 5-11. Other evidence supporting recommendations 1.9.5 and 1.9.6 can be found in the evidence reviews on Drug Combinations and Sequencing (Q).

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Appendices

Appendix A – Review protocols

Review protocol for pharmacological management of asthma in people who are treatment-naïve or receiving SABA-only

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Pharmacological management of Asthma in people who are tlent-naive or receiving SABA-only
2.	Review question	What is the most clinically and cost-effective drug class or combination of drug classes (short-acting beta agonist [SABA] prn, SABA prn plus regular inhaled corticosteroid [ICS], or ICS plus SABA / long-acting beta-agonist [LABA] combination inhaler prn) for the management of asthma in people who are treatment-naïve or receiving SABA alone?
3.	Objective	To determine which drug class or combination of drug classes are most effective to manage asthma in people who are treatment-naïve or receiving SABA-only.
4.	Searches	The following databases (from inception) will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language studies Human studies Other searches: Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.

		Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Asthma
6.	Population	Inclusion: People with a diagnosis of asthma that: • Include those on no asthma therapy • Include those on short acting beta agonist as sole asthma therapy (no limit on duration) • have not yet received preventer/maintenance (inhaled corticosteroids) treatment Strata by age: • 12 years and over • 5-11 years • Under 5 years Exclusion: People who have received preventer (inhaled corticosteroid) treatment People with severe asthma

7.	Intervention	• Short-acting beta agonist [SABA] prn
		  ○ Salbutamol
		  ○ terbutaline
		  ○ SABA prn plus regular inhaled corticosteroid [ICS]budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone)
		• ICS combination inhaler prn
		  ○ Any ICS / formoterol combination inhaler
		  ○ Any ICS with any fast acting SABA combination (salbutamol, terbutaline)
		
		Minimum duration of study treatment 8 weeks

8.	Comparator	Interventions to one another

9.	Types of study to be included	• RCT • Systematic reviews of RCTs Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded Non randomised studies to be excluded
11.	Context	Asthma treatment at primary or secondary care setting. This review question has different interventions and outcomes from previous guideline question and the search will be done from inception rather than update from previous search.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at 3-5 and ≥6 months) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at 3-5 and ≥6 months) • Reliever/rescue medication use (continuous outcome at ≥3 months) • Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and*

		analyse separately (do not extract both). For children, only use FEV1 %pred.
		• Adverse events
		  ○ Linear growth (continuous outcome at ≥1 year),
		  ○ Pneumonia frequency (dichotomous outcome at ≥3 months) (including lower respiratory and general, in that order, respiratory tract infections, but not including upper respiratory tract infections)
		  ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months)
		  ○ Bone mineral density (continuous outcome at ≥6 months)
		• Inflammatory markers; exhaled nitric oxide (FeNO) (continuous outcome at ≥8 weeks)

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0)
15.	Strategy for data synthesis	Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. Where heterogeneity is present within meta-analysed outcomes, studies of very high/high risk of bias rating will be removed from the analysis to as a first step to resolving heterogeneity. If this does not resolve heterogeneity, then sub-group analysis will be applied.
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: ICS Dose: • High vs moderate vs low

<table>
<tr><td></td><td></td><td colspan="3">Treatment status:
• Those who are treatment naïve
• Those already on SABA

Asthma history
• Previous exacerbation
• No previous exacerbation</td></tr>
<tr><td rowspan="7">17.</td><td rowspan="7">Type and method of review</td><td></td><td colspan="2">Intervention</td></tr>
<tr><td></td><td colspan="2">Diagnostic</td></tr>
<tr><td></td><td colspan="2">Prognostic</td></tr>
<tr><td></td><td colspan="2">Qualitative</td></tr>
<tr><td></td><td colspan="2">Epidemiologic</td></tr>
<tr><td></td><td colspan="2">Service Delivery</td></tr>
<tr><td></td><td colspan="2">Other (please specify)</td></tr>
<tr><td>18.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>19.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3"></td></tr>
<tr><td>21.</td><td>Anticipated completion date</td><td colspan="3">31 July 2024</td></tr>
<tr><td rowspan="8">22.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td></td><td></td></tr>
<tr><td>Piloting of the study selection process</td><td></td><td></td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td></td><td></td></tr>
<tr><td>Data extraction</td><td></td><td></td></tr>
<tr><td>Risk of bias (quality) assessment</td><td></td><td></td></tr>
<tr><td>Data analysis</td><td></td><td></td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

5b Named contact e-mail
asthmachronicmanagement@nice.org.uk
@nice.org.uk</td></tr>
</table>

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
24.	Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Qudsia Malik (Senior systematic reviewer) Clare Jones (Senior systematic reviewer) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager) Lisa Miles (Technical Analyst)
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in 'ine with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any chang's to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186
28.	Other registration details	N/A
29.	Reference/URL for published protocol	N/A
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

		notifying registered stakeholders of publication publicising the guidelin' through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	N/A	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status		Ongoing
			Completed but not published
			Completed and published
			Completed, published and being updated
			Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Table 15: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of

Developing NICE guidelines: the manual (2014).(National Institute for Health and Care Excellence)

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'.
- Studies published before 2006 be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 16: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 Dec 2023	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 20 Dec 2023	Randomised controlled trials Systematic review studies Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 20 Dec 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.

12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	Adrenergic beta-2 Receptor Agonists/
25.	((beta or beta2) adj3 agonist*).ti,ab,kf.
26.	(LABA* or SABA*).ti,ab.
27.	(reliever adj2 inhaler*).ti,ab,kf.
28.	Albuterol/ or Terbutaline/
29.	(albuterol or salbutamol or terbutaline or levosalbutamol).ti,ab,kf.
30.	(Airolin or Airomir or Asmasal or Buventol or Inspiryl or Proventil or Salamol or Salbulin or Pulvinal or Ventolin or Proair or Accuneb or Salbair or Brethine or Bricanyl).ti,ab,kf.
31.	Salmeterol Xinafoate/ or Formoterol Fumarate/
32.	(salmeterol or formoterol or eformoterol or vilanterol or bambuterol or olodaterol or indacaterol).ti,ab,kf.
33.	(Serevent or Neoven or Atimos or Foradil or Oxis or Anoro or Duaklir Genuair or Bambec or Oxeol or Striverdi).ti,ab,kf.
34.	Triamcinolone/ or Budesonide/ or Beclomethasone/ or Fluticasone/ or Mometasone Furoate/
35.	(budesonide or beclomethasone or beclometasone or ciclesonide or fluticasone or flunisolide or triamcinolone or mometasone).ti,ab,kf.
36.	((glucocorticosteroid* or glucocorticoid* or corticosteroid* or cocorticoid* or corticoid* or steroid* or preventer) adj2 inhale*).ti,ab,kf.
37.	ICS.ti,ab.
38.	(Asmabec or Clenil Modulite or Qvar or Alvesco or Pulmicort or Flixotide or Novolizer or Asmanex or Aerobid or Flovent or Becotide).ti,ab,kf.
39.	Albuterol, Ipratropium Drug Combination/ or Budesonide, Formoterol Fumarate Drug Combination/ or Fluticasone-Salmeterol Drug Combination/ or Mometasone Furoate, Formoterol Fumarate Drug Combination/
40.	((combination or MART) adj2 inhaler*).ti,ab,kf.
41.	(("maintenance and reliever" or MART or SMART) adj2 (therap* or treatment*)).ti,ab,kf.
42.	(Fostair or Seretide or DuoResp or Symbicort or Relvar or Fobumix or Ventide or Aerocort).ti,ab,kf.
43.	or/24-42
44.	23 and 43
45.	Meta-Analysis/
46.	Meta-Analysis as Topic/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.

49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54
56.	randomized controlled trial.pt.
57.	controlled clinical trial.pt.
58.	randomi#ed.ab.
59.	placebo.ab.
60.	randomly.ab.
61.	clinical trials as topic.sh.
62.	trial.ti.
63.	or/56-62
64.	44 and (55 or 63)

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	*beta 2 adrenergic receptor stimulating agent/
24.	((beta or beta2) adj3 agonist*).ti,ab,kf.
25.	(LABA* or SABA*).ti,ab.

26.	(reliever adj2 inhaler*).ti,ab,kf.
27.	*salbutamol/ or *terbutaline/
28.	(albuterol or salbutamol or terbutaline or levosalbutamol).ti,ab,kf.
29.	(Airolin or Airomir or Asmasal or Buventol or Inspiryl or Proventil or Salamol or Salbulin or Pulvinal or Ventolin or Proair or Accuneb or Salbair or Brethine or Bricanyl).ti,ab,kf.
30.	*salmeterol xinafoate/ or *formoterol fumarate/
31.	(salmeterol or formoterol or eformoterol or vilanterol or bambuterol or olodaterol or indacaterol).ti,ab,kf.
32.	(Serevent or Neoven or Atimos or Foradil or Oxis or Anoro or Duaklir Genuair or Bambec or Oxeol or Striverdi).ti,ab,kf.
33.	*budesonide/ or *beclometasone/ or *ciclesonide/ or *fluticasone/ or *flunisolide/ or *triamcinolone/ or *mometasone furoate/
34.	(budesonide or beclomethasone or beclometasone or ciclesonide or fluticasone or flunisolide or triamcinolone or mometasone).ti,ab,kf.
35.	((glucocorticosteroid* or glucocorticoid* or corticosteroid* or cocorticoid* or corticoid* or steroid* or preventer) adj2 inhale*).ti,ab,kf.
36.	ICS.ti,ab.
37.	(Asmabec or Clenil Modulite or Qvar or Alvesco or Pulmicort or Flixotide or Novolizer or Asmanex or Aerobid or Flovent or Becotide).ti,ab,kf.
38.	*ipratropium bromide plus salbutamol/ or *budesonide plus formoterol/ or *fluticasone propionate plus salmeterol/ or *formoterol fumarate plus mometasone furoate/
39.	((combination or MART) adj2 inhaler*).ti,ab,kf.
40.	(("maintenance and reliever" or MART or SMART) adj2 (therap* or treatment*)).ti,ab,kf.
41.	(Fostair or Seretide or DuoResp or Symbicort or Relvar or Fobumix or Ventide or Aerocort).ti,ab,kf.
42.	or/23-41
43.	22 and 42
44.	random*.ti,ab.
45.	factorial*.ti,ab.
46.	(crossover* or cross over*).ti,ab.
47.	((doubl* or singl*) adj blind*).ti,ab.
48.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
49.	crossover procedure/
50.	single blind procedure/
51.	randomized controlled trial/
52.	double blind procedure/
53.	or/44-52
54.	Systematic Review/
55.	Meta-Analysis/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	cochrane.jw.

63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	43 and (53 or 64)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2
#4.	conference:pt or (clinicaltrials or trialsearch):so
#5.	#3 not #4
#6.	MeSH descriptor: [Adrenergic beta-2 Receptor Agonists] this term only
#7.	((beta or beta2) near/3 agonist*):ti,ab,kw
#8.	(LABA* or SABA*):ti,ab
#9.	(reliever near/2 inhaler*):ti,ab,kw
#10.	MeSH descriptor: [Albuterol] this term only
#11.	MeSH descriptor: [Terbutaline] this term only
#12.	(albuterol or salbutamol or terbutaline or levosalbutamol):ti,ab,kw
#13.	(Airolin or Airomir or Asmasal or Buventol or Inspiryl or Proventil or Salamol or Salbulin or Pulvinal or Ventolin or Proair or Accuneb or Salbair or Brethine or Bricanyl):ti,ab,kw
#14.	MeSH descriptor: [Salmeterol Xinafoate] this term only
#15.	MeSH descriptor: [Formoterol Fumarate] this term only
#16.	(salmeterol or formoterol or eformoterol or vilanterol or bambuterol or olodaterol or indacaterol):ti,ab,kw
#17.	(Serevent or Neoven or Atimos or Foradil or Oxis or Anoro or Duaklir Genuair or Bambec or Oxeol or Striverdi):ti,ab,kw
#18.	MeSH descriptor: [Triamcinolone] this term only
#19.	MeSH descriptor: [Budesonide] this term only
#20.	MeSH descriptor: [Beclomethasone] this term only
#21.	MeSH descriptor: [Fluticasone] this term only
#22.	MeSH descriptor: [Mometasone Furoate] this term only
#23.	(budesonide or beclomethasone or beclometasone or ciclesonide or fluticasone or flunisolide or triamcinolone or mometasone):ti,ab,kw
#24.	((glucocorticosteroid* or glucocorticoid* or corticosteroid* or cocorticoid* or corticoid* or steroid* or preventer) near/2 inhale*):ti,ab,kw
#25.	ICS:ti,ab
#26.	(Asmabec or Clenil Modulite or Qvar or Alvesco or Pulmicort or Flixotide or Novolizer or Asmanex or Aerobid or Flovent or Becotide):ti,ab,kw
#27.	MeSH descriptor: [Albuterol, Ipratropium Drug Combination] this term only
#28.	MeSH descriptor: [Budesonide, Formoterol Fumarate Drug Combination] this term only
#29.	MeSH descriptor: [Fluticasone-Salmeterol Drug Combination] this term only
#30.	MeSH descriptor: [Mometasone Furoate, Formoterol Fumarate Drug Combination] this term only
#31.	((combination or MART) near/2 inhaler*):ti,ab,kw
#32.	(("maintenance and reliever" or MART or SMART) near/2 (therap* or treatment*)):ti,ab,kw
#33.	(Fostair or Seretide or DuoResp or Symbicort or Relvar or Fobumix or Ventide or Aerocort):ti,ab,kw

#34.	(or #6-#33)
#35.	#5 and #34

Epistemonikos search terms

1.	(title:(asthma*) OR abstract:(asthma*)) AND (title:("beta-2 receptor agonist" OR "beta2 receptor agonist" OR "beta-2 agonist" OR "beta2 agonist" OR "beta agonist" OR LABA* OR SABA* OR "reliever inhaler" OR "reliever inhalers" OR albuterol OR salbutamol OR terbutaline OR levosalbutamol OR Airolin OR Airomir OR Asmasal OR Buventol OR Inspiryl OR Proventil OR Salamol OR Salbulin OR Pulvinal OR Ventolin OR Proair OR Accuneb OR Salbair OR Brethine OR Bricanyl OR salmeterol OR formoterol OR eformoterol OR vilanterol OR bambuterol OR olodaterol OR indacaterol OR Serevent OR Neoven OR Atimos OR Foradil OR Oxis OR Anoro OR Duaklir Genuair OR Bambec OR Oxeol OR Striverdi OR budesonide OR beclomethasone OR beclometasone OR ciclesonide OR fluticasone OR flunisolide OR triamcinolone OR mometasone OR "inhaled corticosteroid" OR "inhaled corticosteroids" OR "inhaled steroid" OR "inhaled steroids" OR "preventer inhaler" OR "preventer inhalers" OR ICS OR Asmabec OR Clenil Modulite OR Qvar OR Alvesco OR Pulmicort OR Flixotide OR Novolizer OR Asmanex OR Aerobid OR Flovent OR Becotide OR "combination inhaler" OR "combination inhalers" OR "MART inhaler" OR "MART inhalers" OR "maintenance AND reliever" OR "MART therapy" OR "SMART therapy" OR Fostair OR Seretide OR DuoResp OR Symbicort OR Relvar OR Fobumix OR Ventide OR Aerocort) OR abstract:("beta-2 receptor agonist" OR "beta2 receptor agonist" OR "beta-2 agonist" OR "beta2 agonist" OR "beta agonist" OR LABA* OR SABA* OR "reliever inhaler" OR "reliever inhalers" OR albuterol OR salbutamol OR terbutaline OR levosalbutamol OR Airolin OR Airomir OR Asmasal OR Buventol OR Inspiryl OR Proventil OR Salamol OR Salbulin OR Pulvinal OR Ventolin OR Proair OR Accuneb OR Salbair OR Brethine OR Bricanyl OR salmeterol OR formoterol OR eformoterol OR vilanterol OR bambuterol OR olodaterol OR indacaterol OR Serevent OR Neoven OR Atimos OR Foradil OR Oxis OR Anoro OR Duaklir Genuair OR Bambec OR Oxeol OR Striverdi OR budesonide OR beclomethasone OR beclometasone OR ciclesonide OR fluticasone OR flunisolide OR triamcinolone OR mometasone OR "inhaled corticosteroid" OR "inhaled corticosteroids" OR "inhaled steroid" OR "inhaled steroids" OR "preventer inhaler" OR "preventer inhalers" OR ICS OR Asmabec OR Clenil Modulite OR Qvar OR Alvesco OR Pulmicort OR Flixotide OR Novolizer OR Asmanex OR Aerobid OR Flovent OR Becotide OR "combination inhaler" OR "combination inhalers" OR "MART inhaler" OR "MART inhalers" OR "maintenance AND reliever" OR "MART therapy" OR "SMART therapy" OR Fostair OR Seretide OR DuoResp OR Symbicort OR Relvar OR Fobumix OR Ventide OR Aerocort))

B.2 Health economic literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Asthma population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies and modelling.

Table 17: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling

Database	Dates searched	Search filters and limits applied
	Quality of Life 1946 – 29 Dec 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	Modelling 1974 – 29 Dec 2023	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.

12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.

52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/

17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/
27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.
31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43
45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/
50.	stochastic model/
51.	decision theory/
52.	decision tree/
53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.

57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.
66.	(economic* or pharmaco?economic*).ti.
67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

NHS EED and HTA (CRD) search terms

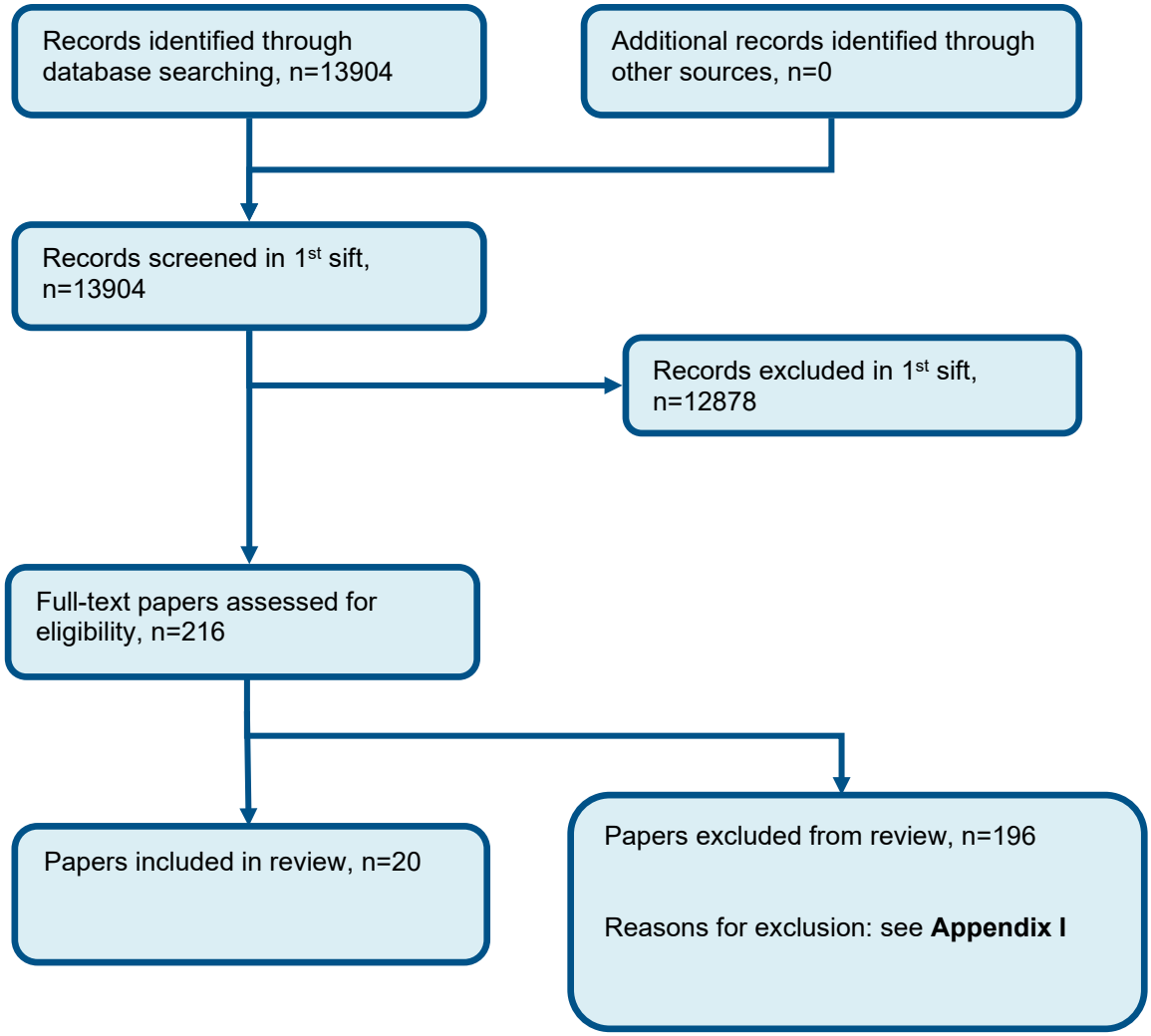
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

INAHTA search terms

1.	(Asthma)[mh] OR (asthma*)[Title] OR (asthma*)[abs]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of drug classes for initial asthma management



Appendix D – Effectiveness evidence

Bateman, 2021

Bibliographic Reference	Bat'man, E. D.; O'Byrne, P. M.; FitzGerald, J. M.; Barnes, P. J.; Zheng, J.; Lamarca, R.; Puu, M.; Parikh, H.; Alagappan, V.; Reddel, H. K.; Positioning As-needed Budesonide-Formoterol for Mild Asthma: Effect of Prestudy Treatment in Pooled Analysis of SYGMA 1 and 2; Annals of the American Thoracic Society; 2021; vol. 18 (no. 12); 2007-2017

Study details

Secondary publication of another included study- see primary study for details	Secondary pu'lication of O'Byrne (2018) SYGMA 1 and Bateman (2018) SYGMA 2 analysing only participants who had not received ICS pre-trial
Other publications associated with this study included in review	No additional information
Trial name / registration number	SYGMA 1 (NCT022149199) and SYGMA 2 (NCT02224157)
Study type	Randomised controlled trial (RCT)
Study location	Multi-national
Study setting	No additional information

Study dates	SYGMA–1: July 2014 - August 2017 SYGMA 2: –ovember 2014 - August 2017
Sources of funding	Funded by AstraZeneca
Inclusion criteria	Outpatients of either gender aged ≥12 years at Visit 1 Diagnosis of asthma according to Global Initiative for Asthma (GINA) criteria based on symptoms with a documented history of at least 6 months prior to Visit 1 Lung function and reversibility tests performed as part of Visit 2 and 3 can be used as a confirmation of asthma diagnosis according to GINA criteria if there is no measure of lung function available before Visit 1 Patients who are in need of GINA (2012) Step 2 treatment: - uncontrolled on inhaled short-acting bronchodilator(s) 'as needed' (short-acting β2-agonist [SABA] and/or short-acting anticholinergic agent) as judged by the investigator for the last 30 days befor– Visit 2, or - controlled on mono-mainte–ance therapy - with low stable dose inhaled glucocorticoid (≤400 µg budesonide per day or corresponding inhaled dose of other agent) or leukotriene receptor anta–onist (LTRA) - in addition to 'as needed' use of inhaled short-acting bronchodilator(s) (SABA and/or short-acting anticholinergic agent), as judged by the investigator for the last 30 days prior to Visit 2 Based on lung function tests (forced expiratory volume in 1 second [FEV1] and forced vital capacity assessed by spirometry) at Visit 2, patients pre-treated with: - an inhaled short-acting bronchodilator only should have pre-bronchodilator FEV1 ≥60% predicted and post-bronchodilator FEV1 ≥80% predicted according to the European Respiratory Society (ERS–guidelines1 - low-dose inhaled glucocorticoid or LTRA medication in addition to inhaled short-acting bronchodilator(s) should have pre-bronchodilator FEV1 ≥80% predicted according to the ERS guidelines Reversible airway obstruction according to a reversibility test performed at Visit 2 defined as an increase in FEV1 ≥12% and 200 mL relative to baseline, after inhalation of 1 mg terbutaline Turbuhaler®. The test can be repeated at Visit 3 in case the patients fail at Visit 2. If patients fail at both occasions, they can still be included if they have a documented historical reversibility within the last 12 months prior to Visit 3, with an increase in FEV1 ≥12% and 200 mL relative to baseline after administration of a rapid-acting β2-agonist

	Use of terbutaline Turbuhaler® ‘as needed’ due to asthma symptoms on at least 3 separate days during the last week of the run-in period Ability to use Turbuhaler® correctly
Exclusion criteria	Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site) Previous randomization in the present study Participation in another clinical study with a non-biologic investigational product or new formulation of a marketed non-biologic drug during the last 30 days prior to Visit 1 Participation in another clinical trial with any marketed or investigational biologic drug within 4 months or 5 half-lives whichever is longer, prior to Visit 1 Any asthma worsening requiring change in asthma treatment other than inhaled short-acting bronchodilator(s) (SABA and/or short-acting anticholinergic agent) within 30 days prior to Visit 1 Use of oral, rectal, or parenteral glucocorticoid within 30 days and/or depot parenteral glucocorticoid within 12 weeks prior to Visit 1 Use of any β-blocking agent including eye-drops 8. Known or suspected hypersensitivity to study drugs or excipient Smoker (current or previous) with a smoking history of ≥10 pack-years Medical history of life-threatening asthma including intubation and intensive care unit admission Any significant disease or disorder (e.g., cardiovascular, pulmonary other than asthma, gastrointestinal, hepatic, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient’s ability to participate in the study

	Any clinically relevant abnormal findings in physical examination and/or vital signs at Visit 2, which, in the opinion of the investigator, may put the patient at risk if participating in the study Pregnancy, breast-feeding, or planned pregnancy during the study. Fertile women not using acceptable contraceptive measures, as judged by the investigator Planned hospitalization during the study Suspected poor capability, as judged by the investigator, of following instructions of the study Use of ≥6 terbutaline Turbuhaler® 'as needed' inhalations per day, for a certain number of days depending on the actual length of run-in: for ≥2 days out of 14 days; for ≥3 days out of 15–21 days; for ≥4 days out of 22 or more days of run-in Any asthma worsening requiring change in asthma treatment other than inhaled short-acting bronchodilator(s) (SABA and/or short-acting anticholinergic agent) from Visit 1 until Visit 2 and/or requiring any asthma treatment other than run-in study medication from Visit 2 until randomization
Recruitment / selection of participants	No additional information
Intervention(s)	Both SYGMA 1 and 2 had a 2-4 week run in period where participants received terbutaline (0.5 mg) as needed for symptoms. To progress to randomisation, participants must have had an indication for step 2 treatment by using terbutaline as needed on at least 3 days during the last week of the run in period and by not having used at least 6 inhalations per day for 2, 3 or 4 (for 2, 3 and 4 week run in periods, respectively) or more days in the run in period. **SYGMA 1:** Participants were randomised to receive one of three regimens: • twice daily placebo plus terbutaline (0.5 mg) as needed (SABA) • twice daily placebo plus budesonide-formoterol (200/6 ug) as needed (ICS combination) • twice daily budesonide (200 ug) plus terbutaline (0.5 mg) as needed (ICS+SABA)

	During the trial, participants who had asthma exacerbations or long-term poor asthma control were permitted to receive additional treatment with open-label budesonide at a dose of 200 ug twice daily for 2-4 weeks, or longer at the investigator's discretion. All inhaled steroid prescription was recorded and use of all trial medications were monitored using an inhaler monitor (Turbuhaler) **SYGMA 2:** Participants were randomised to receive one of two regimens: • twice daily placebo plus budesonide-formoterol (200/6 ug) as needed (ICS combination) • twice daily budesonide (200 ug) plus terbutaline (0.5 mg) as needed (ICS+SABA) Use of all medications was recorded throughout using an inhaler monitor (Turbuhaler)
Population subgroups	**Treatment status:** SABA as needed **Asthma history:** not reported
Comparator	All study arms were compared to one another
Number of participants	**S–GMA 1:** SABA - 565 IC– combination -–565 ICS+SABA - 576 **SYGMA 2:**

	IC– combination - 959 ICS+SABA- 975
Duration of follow-up	12 months
Indirectness	No additional information
Additional comments	No additional information

Study arms

ICS combination inhaler (N = 1524)
Participants received budesonide/formoterol (200/6 ug) as needed

ICS+SABA (N = 1551)
Participants received regular twice-daily budesonide (200 ug) plus as needed terbutaline (0.5 mg)

SABA (N = 565)
Participants received placebo plus terbutaline (0.5 mg) as needed

Characteristics

Arm-level characteristics

Characteristic	ICS combination inhaler (N = 1524)	ICS+SABA (N = 1551)	SABA (N = 565)
% Female Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
SYGMA 1 ICS combination n=576, ICS+SABA n=565, SABA n=565 Sample size	n = 338 ; % = 59.8	n = 346 ; % = 60.1	n = 337 ; % = 59.6
SYGMA 2 ICS combination n=959, ICS+SABA n=975 Sample size	n = 582 ; % = 60.7	n = 584 ; % = 59.9	n = NA ; % = NA
Mean age (SD) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
SYGMA 1 ICS combination n=576, ICS+SABA n=565, SABA n=565 Mean (SD)	39.4 (16.3)	38.1 (17)	39 (16.4)
SYGMA 2 ICS combination n=959, ICS+SABA n=975 Mean (SD)	39.5 (16.4)	38.8 (16.2)	NA (NA)
Ethnicity Nominal	NR	NR	NR

Characteristic	ICS combination inhaler (N = 1524)	ICS+SABA (N = 1551)	SABA (N = 565)
Comorbidities Nominal	NR	NR	NR
1 or more severe exacerbations in past 12 months Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
SYGMA 1 ICS combination n=576, ICS+SABA n=565, SABA n=565 Sample size	n = 108 ; % = 19.1	n = 118 ; % = 20.5	n = 106 ; % = 18.8
SYGMA 2 ICS combination n=959, ICS+SABA n=975 Sample size	n = 241 ; % = 25.1	n = 241 ; % = 24.7	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	ICS combination inhaler, Baseline, N = 1524	ICS combination inhaler, 12 month, N = 1431	ICS+SABA, Baseline, N = 1551	ICS+SABA, 12 month, N = 1462	SABA, Baseline, N = 565	SABA, 12 month, N = 545
Asthma control (Asthma Control Questionnaire-5) scale range 0-6, change scores Mean (95% CI)	NA (NA to NA)	-0.37 (-0.4 to -0.34)	NA (NA to NA)	-0.44 (-0.48 to -0.42)	NA (NA to NA)	-0.21 (-0.26 to -0.16)
Lung Function (% predicted FEV1) change scores (ICS combination n=1465, ICS+SABA n=1486) Mean (95% CI)	NA (NA to NA)	2.2 (1.7 to 2.7)	NA (NA to NA)	3.4 (2.9 to 3.9)	NA (NA to NA)	-0.2 (-1 to 0.6)

Asthma control (Asthma Control Que–tionnaire—) - Polarity - Lower values are better
Lung Function (% pr–dicted FEV–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	ICS combination inhaler, Baseline, N = 1524	ICS combination inhaler, 12 month, N = 1524	ICS+SABA, Baseline, N = 1551	ICS+SABA, 12 month, N = 1551	SABA, Baseline, N = 565	SABA, 12 month, N = 565
Severe asthma exacerbations number of patients with at least 1 exacerbation No of events	n = NA ; % = NA	n = 95 ; % = 6.2	n = NA ; % = NA	n = 129 ; % = 8.3	n = NA ; % = NA	n = 51 ; % = 9

Outcome	ICS combination inhaler, Baseline, N = 1524	ICS combination inhaler, 12 month, N = 1524	ICS+SABA, Baseline, N = 1551	ICS+SABA, 12 month, N = 1551	SABA, Baseline, N = 565	SABA, 12 month, N = 565
Adverse events (any adverse event) final values No of events	n = NA ; % = NA	n = 597 ; % = 39.2	n = NA ; % = NA	n = 665 ; % = 42.9	n = NA ; % = NA	n = 236 ; % = 41.8
Mortality (adverse events leading to death) final values No of events	n = NA ; % = NA	n = 1 ; % = 0.07	n = NA ; % = NA	n = 2 ; % = 0.13	n = NA ; % = NA	n = 0 ; % = 0

Severe asthma –xacerbatio–s - Polarity - Lower values are better
Adverse events (any a–verse even–) - Polarity - Lower values are better
Mortality (adverse events lead–ng to deat–) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes SYGMA1 – Asthma control (Asthma Control Questionnaire-5) – Mean (95% –CI) - ICS combination inhaler-ICS+SABA-SABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unclear method of randomisation and allocation concealment; limited information on statistical methods used to account for switching groups; No information on handling of switching groups (switching likely due to clinician being able to add ICS to SABA treatment arm if exacerbations occurred))*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes SYGMA1 – Lung Function (% predicted FEV1) – Mean (95% –CI) - ICS combination inhaler-ICS+SABA-SABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations —No Of Events - ICS combination inhaler-ICS+SABA-SABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unclear method of randomisation and allocation concealment; Limited information on statistical methods used*

Section	Question	Answer
		to account for switching groups; No information on handling of switching groups (switching likely due to clinician being able to add ICS to SABA treatment arm if exacerbations occurred))
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events (any adverse event) —No Of Events - ICS combination inhaler-ICS+SABA-SABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unclear method of randomisation and allocation concealment; Limited information on statistical methods used to account for switching groups; No information on handling of switching groups (switching likely due to clinician being able to add ICS to SABA treatment arm if exacerbations occurred))*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Mortality (adverse events leading to death) —No Of Events - ICS combination inhaler-ICS+SABA-SABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on handling of switching groups (switching likely due to clinician being able to add ICS to SABA treatment arm if exacerbations occurred); Limited information on statistical methods used to account for switching groups)*
Overall bias and Directness	Overall Directness	Directly applicable

Beasley, 2019

Bibliographic Reference	Beasley, R.; Holliday, M.; Reddel, H. K.; Braithwaite, I.; Ebmeier, S.; Hancox, R. J.; Harrison, T.; Houghton, C.; Oldfield, K.; Papi, A.; Pavord, I. D.; Williams, M.; Weatherall, M.; Novel, Start Study Team; Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma; New England Journal of Medicine; 2019; vol. 380 (no. 21); 2020-2030

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Novel START (ACTRN12615000999538)
Study type	Randomised controlled trial (RCT)
Study location	New Zealand, United Kingdom, Italy and Australia
Study setting	Primary and secondary care centers
Study dat–s	March 2016 - August 2017
Sources of funding	Supported by research grants from AstraZeneca (ESR14/10452) and the Health Research Council of New Zealand (18/002)
Inclusion criteria	18-75 years old

	Self-reported diagnosis of asthma from a doctor Use of a SABA as the sole asthma therapy in the previous 3 months and patient report of the use of the SABA on at least two occasions, but on an average of two or fewer occasions per day in the previous 4 weeks (no minimum requirement for patients who had a severe exacerbation within previous 12 months)
Exclusion criteria	Hospitalization for asthma in the previous 12 months Self-reported ICS, LABA, leukotriene receptor agonist, theophylline, anticholinergic agent or cromone as regular maintenance therapy in the 3 months prior to the study Either a patient-reported smoking history of more than 20 pack-years or the onset of respiratory symptoms after the age of 40 years in current or previous smokers with a smoking history of at least 10 pack-years Previous admission to ICU with life-threatening asthma Treatment with oral prednisone in the 6 weeks prior to the study Home supply of prednisone for asthma treatment Self-reported diagnosis of COPD, bronchiectasis or interstitial lung disease Pregnant/breast feeding, or planning to within the study period Self-reported congestive heart failure, unstable coronary heart disease, atrial fibrillation or other clinically significant cardiac disease FEV <50%

Recruitment / selection of participants	No additional information
Intervention(s)	Patients in the albuterol group received albuterol (Ventolin, GlaxoSmithKline), 100 µg, with two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide maintenance group received budesonide (Pulmicort Turbuhaler, AstraZeneca), 200 µg, one inhalation twice daily, plus albuterol (Ventolin), 100 µg, two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide–formoterol group received budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca), 200 µg of budesonide and 6 µg of formoterol, one inhalation as needed for symptom relief. Patients were provided with asthma action plans that included instructions that specified the circumstances under which they should seek medical evaluation for worsening asthma as well as a log for recording urgent medical visits and use of systemic glucocorticoids. Electronic inhaler usage monitors (Adherium), which record the date and time of inhaler actuations were incorporated in all inhalers dispensed in the trial.
Population subgroups	**Treatment status:** SABA as the sole asthma therapy in the previous 3 months; use of SABA on at least two occasions, but on an average of two or fewer occasions per day in the previous 4 week **Asthma history:** not reported
Comparator	Patients in the albuterol group received albuterol (Ventolin, GlaxoSmithKline), 100 µg, with two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide maintenance group received budesonide (Pulmicort Turbuhaler, AstraZeneca), 200 µg, one inhalation twice daily, plus albuterol (Ventolin), 100 µg, two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide–formoterol group received budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca), 200 µg of budesonide and 6 µg of formoterol, one inhalation as needed for symptom relief. Patients were provided with asthma action plans that included instructions that specified the circumstances under which they should seek medical evaluation for worsening asthma as well as a log for recording urgent medical visits and use of systemic glucocorticoids. Electronic inhaler usage monitors (Adherium), which record the date and time of inhaler actuations were incorporated in all inhalers dispensed in the trial.

Number of participants	668 randomised, 209 completed (total) 226 randomised, 117 completed (SABA) 227 randomised, 133 completed (ICS + SABA) 222 randomised, 153 completed (ICS Combination inhaler)
Duration of follow-up	52 weeks
Indirectness	No additional information
Additional comments	Intention to treat

Study arms

SABA (N = 223)
Albuterol (100mcg, two inhalations from pMDI) as needed for symptom relief

ICS + SABA (N = 225)
Budesonide (200mcg, one inhalation twice per day) + albuterol (100mcg, two inhalations from pMDI) as needed for symptom relief

ICS Combination Inhaler (N = 220)
Budesonide (200mcg) / formoterol (6mcg) in a single inhalation as needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	SABA (N = 223)	ICS + SABA (N = 225)	ICS Combination Inhaler (N = 220)
% Female Sample size	n = 113 ; % = 50.7	n = 129 ; % = 57.3	n = 122 ; % = 55.5
Mean age (SD) Mean (SD)	35.8 (14)	34.9 (14.3)	36 (14.1)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
≥1 severe exacerbation in past 12 months Sample size	n = 20 ; % = 9	n = 17 ; % = 7.6	n = 12 ; % = 5.5

Outcomes

Study timepoints

- Baseline
- 52 week

Continuous Outcomes

Outcome	SABA , Baseline, N = 223	SABA , 52 week, N = 223	ICS + SABA, Baseline, N = 225	ICS + SABA, 52 week, N = 225	ICS Combination Inhaler, Baseline, N = 220	ICS Combination Inhaler, 52 week, N = 220
Reliever medication use (number of beta-2-agonist-containing actuations per day) Final values Mean (SD)	NA (NA)	1.01 (1.6)	NA (NA)	0.52 (1.03)	NA (NA)	0.53 (0.54)
Inflammatory markers (FeNO) (Parts per billion (ppb)) Final values (52 week measure: SABA n=193, SABA+ICS n=196, ICS combi n=194) Mean (SD)	55.18 (44.95)	48.69 (38.15)	54.32 (44)	35.92 (32.23)	50.8 (46.05)	37.65 (34.19)
Asthma control (Asthma Control Questionnaire-5) Scale range 0-6, final values (baseline measure: SABA n=222, 52 week measure: SABA n=197, SABA+ICS n=197, ICS combi n=196) Mean (SD)	1.1 (0.7)	0.9 (0.9)	1.1 (0.7)	0.7 (0.8)	1.1 (0.7)	0.8 (0.7)
Lung Function (% predicted FEV1) Final values (52 week measure: SABA n=196, SABA+ICS n=197, ICS combi n=195) Mean (SD)	89.2 (13.7)	89.1 (13.9)	90.3 (13.6)	91.2 (13.8)	89.8 (14.1)	91.4 (14.1)

Reliever medication use (number of beta-2-agonist-containing actuat–ons per da–) - Polarity - Lower values are better
Inflammatory m–rkers (FeN–) - Polarity - Lower values are better
Asthma control (Asthma Control Que–tionnaire-–) - Polarity - Lower values are better
Lung Function (% pr–dicted FEV–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA , Baseline, N = 223	SABA , 52 week, N = 223	ICS + SABA, Baseline, N = 225	ICS + SABA, 52 week, N = 225	ICS Combination Inhaler, Baseline, N = 220	ICS Combination Inhaler, 52 week, N = 220
Severe asthma exacerbations (requiring course of systemic glucocorticoids) Final values No of events	n = NA ; % = NA	n = 23 ; % = 10.31	n = NA ; % = NA	n = 21 ; % = 9.33	n = NA ; % = NA	n = 9 ; % = 4.09

Severe asthma exacerbations (requiring course of systemic glu–ocorticoid–) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Reliever medication use

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Inflammatory markers

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

Asthma control

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Lung function

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Severe asthma exacerbations

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Berger, 2002

Bibliographic Reference	Berger, W. E.; Ford, L. B.; Mahr, T.; Nathan, R. A.; Crim, C.; Edwards, L.; Wightman, D. S.; Lincourt, W. R.; Rickard, K.; Efficacy and safety of fluticasone propionate 250 mug administered once daily in patients with persistent asthma treated with or without inhaled corticosteroids; Annals of Allergy, Asthma and Immunology; 2002; vol. 89 (no. 4); 393-399

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	48 clinical centres
Study dates	No additional information
Sources of funding	Supported by GlaxoSmithKline
Inclusion criteria	Aged ≥12 years

	Non-smokers Asthma (defined by ATS criteria) requiring pharmacotherapy for at least 6 months Treated with only bronchodilators or theophylline for at least one-month FEV1 60-85% of predicted and a 12% increase after receiving SABA at screening, and FEV1 within 15% of screening value at the end of the run-in Used albuterol on ≥2 of the last 7 days of the run-in
Exclusion criteria	Life threatening or unstable asthma Other clinically significant uncontrolled disease Chickenpox within 3 weeks Current respiratory infection Smoking history >10 pack years Concomitant use of any other medication that could interfere with study medications Use of corticosteroids, LABAs, cromolyn, nedocromil, anticholinergics or leukotriene modifiers
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 2-week run-in period, participants allocated to the intervention received 250 mcg fluticasone propionate once per day in the morning in additional to albuterol as-needed
Population subgroups	**Treatment status**

	Receiving SABA **Asthma history** Not reported
Comparator	Following a 2-week run-in period, participants allocated to the comparator received a placebo inhaler that was taken once per day in the morning in additional to albuterol as-needed
Number of participants	SABA plus ICS: 198 allocated SABA: 210 allocated, Study also contained 401 participants who had previously been tre–ted with ICS - excluded from this review as no washout period was applied prior to study entry
Duration of follow-up	12 weeks
Indirectness	Downgraded by one increment due to population–indirectness - participants could have been receiving theophylline prior to study entry, but no information on number receiving
Additional comments	Intention to treat with last observation carried forward

Study arms

SABA prn plus regular ICS (N = 198)
250 mcg fluticasone propionate once per day plus SABA as-needed

SABA prn (N = 210)
Placebo inhaler once per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 198)	SABA prn (N = 210)
% Female Sample size	n = 115 ; % = 58	n = 134 ; % = 64
Mean age (SD) Mean (range) Nominal	33	33
Mean age (SD) Mean (range) Range	12 to 74	12 to 69
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SE)	72 (7.3)	71.9 (6.9)

Characteristic	SABA prn plus regular ICS (N = 198)	SABA prn (N = 210)
Asthma control (Puffs per day) SABA use Mean (SE)	3.63 (0.18)	3.55 (0.17)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 198	SABA prn plus regular ICS, 12 week, N = 198	SABA prn, Baseline, N = 210	SABA prn, 12 week, N = 210
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 3 ; % = 2	n = NA ; % = NA	n = 12 ; % = 6

Severe asthma –xacerbatio–s - Polarity - Lower values are better

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 198	SABA prn plus regular ICS, 12 week, N = 198	SABA prn, Baseline, N = 210	SABA prn, 12 week, N = 210
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-1.6 (2.8)	NA (NA)	-0.9 (2.5)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.23 (0.42)	NA (NA)	0.1 (0.43)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	34.3 (61.9)	NA (NA)	12.2 (46.4)

Reliever/rescue m–dication u–e - Polarity - Lower values are better
Lung Fu–ction (FEV–) - Polarity - Higher values are better
Lung f–nction (PE–) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Severe asthma exacerbations —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Reliever/rescue medication use— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Lung function (PEF)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Boonsawat, 2008

Bibliographic Reference	Boonsawat, W.; Goryachkina, L.; Jacques, L.; Frith, L.; Combined salmeterol/fluticasone propionate versus fluticasone propionate alone in mild asthma : a placebo-controlled comparison; Clinical Drug Investigation; 2008; vol. 28 (no. 2); 101-11

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	Primary care and hospital outpatient
Study dates	No additional information
Sources of funding	Sponsored by GlaxoSmithKline
Inclusion criteria	Diagnosed with asthma for at least 6 months

	Aged 12-79 years Receiving SABA monotherapy PEF ≥80% of predicted Daytime symptom score ≥1 on 3-6 days of the past 7 days PEF reversibility ≥15% following salbutamol administration or mean morning PEF <85% of post-salbutamol value in the 7 days prior to study entry
Exclusion criteria	Received ICS or leukotriene antagonists within 12 weeks Received LABAs, sodium cromoglicate, nedocromil, anticholinergic bronchodilators or methylxanthines within 2 weeks Respiratory tract infection within 4 weeks Acute asthma exacerbation within 12 weeks Smoking history greater than 10 pack years Pregnant or lactating Daily symptoms/SABA use
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 2-week run-in period where all participants had their current therapy discontinued and received salbutamol as-needed, those allocated to the intervention received 100 mcg fluticasone propionate once per day in the morning plus salbutamol as-needed

	Concomitant medications None allowed, except for oral prednisolone for treatment of exacerbations *Study also included an arm where participants received reg–lar ICS/LABA - excluded from this review due to not containing a relevant intervention*
Population subgroups	**Treatment status** Receiving SABA **Asthma history** Not reported
Comparator	Following a 2-week run-in period where all participants had their current therapy discontinued and received salbutamol as-needed, those allocated to the comparator received placebo once per day in the morning plus salbutamol as-needed **Concomitant medications** None allowed, except for oral prednisolone for treatment of exacerbations
Number of participants	SABA plus regular ICS: 154 allocated, 145 completed SABA: 155 allocated, 144 completed
Duration of follow-up	12 weeks
Indirectness	None

Additional comments	Intention to treat analysis

Study arms

SABA prn plus regular ICS (N = 154)
100 mcg fluticasone propionate once per day plus salbutamol as-needed

SABA prn (N = 155)
Placebo plus salbutamol as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 154)	SABA prn (N = 155)
% Female Sample size	n = 87; % = 56	n = 72; % = 46
Mean age (SD) Mean (range) Nominal	34	33.4
Mean age (SD) Mean (range) Range	12 to 68	12 to 73

Characteristic	SABA prn plus regular ICS (N = 154)	SABA prn (N = 155)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	96 (15.2)	96.1 (15.3)
Asthma control (%) Median (range) rescue-free days in week before trial Nominal	57.14	57.14
Asthma control (%) Median (range) rescue-free days in week before trial Range	0 to 100	0 to 100

Outcomes

Study timepoints

- Baseline
- 12 week

Contrast Outcomes

Outcome	SABA prn plus regular ICS vs SABA prn, Baseline, N2 = 155, N1 = 154	SABA prn plus regular ICS vs SABA prn, 12 week, N2 = 155, N1 = 154
Lung function (PEF) (L/min) Change scores Mean (95% CI)	NA (NA to NA)	9 (1 to 16.2)

Lung f–nction (PE–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 154	SABA prn plus regular ICS, 12 week, N = 154	SABA prn, Baseline, N = 155	SABA prn, 12 week, N = 155
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 8 ; % = 5.2	n = NA ; % = NA	n = 12 ; % = 7.7
Adverse events Final values No of events	n = NA ; % = NA	n = 57 ; % = 37	n = NA ; % = NA	n = 74 ; % = 48

Severe asthma –xacerbatio–s - Polarity - Lower values are better
A–verse even–s - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contrast Outcomes – Lung function (PEF) – Mean (95%) CI-SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to maintenance treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to maintenance treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to maintenance treatment not monitored)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Chavasse, 2001

Bibliographic Reference	Chavasse, R. J.; Bastian-Lee, Y.; Richter, H.; Hilliard, T.; Seddon, P.; Persistent wheezing in infants with an atopic tendency responds to inhaled fluticasone; Archives of Disease in Childhood; 2001; vol. 85 (no. 2); 143-8

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Hospital outpatient clinics and GP referrals

Study dates	No additional information
Sources of funding	Supported by GlaxoWellcome
Inclusion criteria	Aged 3 to 12 months Documented history of: • Persistent wheeze (≥3 days/week for ≥6 weeks) • Persistent cough (≥3 nights/week for ≥6 weeks) • Recurrent wheeze (≥3 occasions in past 3 months) Personal history of eczema or family history of atopy in first degree relative
Exclusion criteria	History of preterm birth before 34 weeks gestation Required period of mechanical ventilation Major congenital malformation Already regularly using inhaled corticosteroids or received oral corticosteroids within a month (deferred entry until one-month had passed)
Recruitment / selection of participants	Recruited from hospital outpatient clinics, GP referrals and a small number following ward admission due to wheezing
Intervention(s)	Following a two-week run-in period, participants allocated to the intervention received 50 mcg fluticasone propionate, three inhalations twice per day plus salbutamol as-needed
Population subgroups	**Treatment status** Not reported

	Asthma history Not reported
Comparator	Following a two-week run-in period, participants allocated to the comparator received a placebo inhaler which was taken as three inhalations twice per day plus salbutamol as-needed
Number of participants	SABA plus ICS: 19 completed SABA: 18 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Per protocol analysis. Study initially contained 52 participants, 15 of which are not included in the analysis due to not completing diaries for the complete treatment period

Study arms

SABA prn plus regular ICS (N = 19)
50 mcg fluticasone propionate, three inhalations twice per day plus SABA as-needed

SABA prn (N = 18)
Placebo inhaler, one inhalation twice per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 19)	SABA prn (N = 18)
% Female Sample size	n = 6 ; % = 32	n = 4 ; % = 22
Mean age (SD) (Months) Mean (SD)	9.8 (2.6)	8.9 (2.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function Nominal	NR	NR
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 19	SABA prn plus regular ICS, 12 week, N = 19	SABA prn, Baseline, N = 18	SABA prn, 12 week, N = 18
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-0.22 (0.57)	NA (NA)	0.12 (1.02)

Reliever/rescue m–dication u–e - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use—- Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence to regular treatment not monitored and 29% dropout rate with reasons potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Chuchalin, 2008

Bibliographic Reference	Chuchalin, A.; Jacques, L.; Frith, L.; Salmeterol/fluticasone propionate via DiskusTM once daily versus fluticasone propionate twice daily in patients with mild asthma not previously receiving maintenance corticosteroids; Clinical Drug Investigation; 2008; vol. 28 (no. 3); 169-181

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	Outpatient
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	Aged 12-79 years

	Diagnosis of asthma for at least 6 months Receiving only SABA as-needed PEF ≥80% of predicted PEF reversibility ≥15% Mean morning PEF <85% of post-bronchodilator value Daytime symptom score ≥1 on 3-6 of 7 days prior to study entry
Exclusion criteria	Received inhaled, oral, parenteral or depot corticosteroids or leukotriene antagonists within 12 weeks Received LABAs, sodium cromoglicate, nedocromil, ketotifen or oral beta-2-adrenoceptor agonists within 2 weeks Smoking history greater than 10 pack years Respiratory tract infection with 4 weeks Pregnant or lactating
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 2-week run-in period, those allocated to the intervention received 100 mcg fluticasone propionate twice per day, once in the morning and once in the evening along with salbutamol as-needed **Concomitant medications** None allowed except oral prednisolone for exacerbation treatment

	Study also included an arm where participants received reg–lar ICS/LABA - excluded from this review due to not containing a relevant intervention
Population subgroups	**Treatment status** Receiving SABA **Asthma history** Not reported
Comparator	Following a 2-week run-in period, those allocated to the comparator received placebo twice per day, once in the morning and once in the evening along with salbutamol as-needed **Concomitant medications** None allowed except oral prednisolone for exacerbation treatment
Number of participants	SABA plus ICS: 970 allocated, 860 completed SABA: 315 allocated, 260 completed
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	Intention to treat analysis

Study arms

SABA prn plus regular ICS (N = 970)
100 mcg fluticasone propionate, one inhalation twice per day, plus salbutamol as-needed

SABA prn (N = 315)
Placebo twice per day plus salbutamol as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 970)	SABA prn (N = 315)
% Female Sample size	n = 563 ; % = 58	n = 192 ; % = 61
Mean age (SD) Mean (range) Nominal	33.8	35
Mean age (SD) Mean (range) Range	12 to 76	12 to 78
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	SABA prn plus regular ICS (N = 970)	SABA prn (N = 315)
White Sample size	n = 669 ; % = 69	n = 221 ; % = 70
Black Sample size	n = 10 ; % = 1	n = 3 ; % = 1
Asian Sample size	n = 213 ; % = 22	n = 72 ; % = 23
Other Sample size	n = 68 ; % = 7	n = 25 ; % = 8
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	96.1 (14.2)	98 (19)
Asthma control (Inhalations) Mean (range) 24-h SABA use Nominal	0.57	0.57
Asthma control (Inhalations) Mean (range) 24-h SABA use Range	0 to 3.1	0 to 3.6

Outcomes

Study timepoints

- Baseline
- 52 week

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 970	SABA prn plus regular ICS, 52 week, N = 970	SABA prn, Baseline, N = 315	SABA prn, 52 week, N = 315
Adverse events Final values No of events	n = NA ; % = NA	n = 568 ; % = 58.6	n = NA ; % = NA	n = 190 ; % = 60.3
Pneuomonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 40 ; % = 4	n = NA ; % = NA	n = 15 ; % = 5

A–verse even–s - Polarity - Lower values are better
Pneuomonia (respiratory trac– infection–) - Polarity - Lower values are better

Contrast Outcomes

Outcome	SABA prn plus regular ICS vs SABA prn, Baseline, N2 = 315, N1 = 970	SABA prn plus regular ICS vs SABA prn, 52 week, N2 = 315, N1 = 970
Lung function (PEF) (L/min) Change scores Mean (95% CI)	NA (NA to NA)	20.1 (14.7 to 25.5)

Lung f–nction (PE–) - Polarity - Higher values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Adverse events —No Of Events - SABA prn plus regular ICS-SABA prn-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to regular treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Cont–ast Outcomes - Lung function (PEF) – Mean (95% –CI) - SABA prn plus regular ICS-SABA prn-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to regular treatment not monitored, 13% dropout rate, 6% difference between dropout rates between arms and reasons for discontinuation related 'o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneuomonia (respiratory tract infections) —No Of Events - SABA prn plus regular ICS-SABA prn-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to regular treatment not monitored)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Galant, 1996

Bibliographic Reference	Galant, S. P.; Lawrence, M.; Meltzer, E. O.; Tomasko, M.; Baker, K. A.; Kellerman, D. J.; Fluticasone propionate compared with theophylline for mild-to-moderate asthma; Annals of Allergy, Asthma, & Immunology; 1996; vol. 77 (no. 2); 112-8

Study details

Secondary publication of	No additional information

another included study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Glaxo Research Institute
Inclusion criteria	Aged ≥12 years Stable, reversible asthma Required daily drug treatment for asthma Serum trough theophylline concentration <3.5 mg/L FEV1 45-75% of predicted and ≥15% increase after receiving SABA at screening, and 45-65% of predicted or 65-75% with additional symptoms (>1 day with >8 SABA uses, >2 days with >20% PEF variability, total weekly symptom score >7 on any symptom, 2-4 night time awakenings due to asthma) at the end of the run-in >70% compliant to medications provided during run-in

	Not pregnant Surgically sterile, ≥1 year post-menopausal or using birth control for ≥3 months
Exclusion criteria	History of life-threatening asthma Smoking within a year or a history >10 pack years Use of inhaled or intranasal corticosteroids within 4 weeks, oral or injectable corticosteroids within 3 months or alternate-day oral steroids for more than 2 months in the past 2 years
Recruitment / selection of participants	Recruited from 19 centres, method not reported
Intervention(s)	Following a 1-week run-in period where participants received placebo ICS and theophylline, those allocated to the intervention arms received one of two treatment regimes (both contained theophylline placebos): • 25 mcg fluticasone propionate, two inhalations twice per day (100 mcg) plus albuterol as-needed • 50 mcg fluticasone propionate, two inhalations twice per day (200 mcg) plus albuterol as-needed *Two study arms combined for this review*

	Study also included an arm containing–theophylline - excluded from this review due to not containing a relevant intervention
Population subgroups	**Treatment status** Receiving SABA **Asthma history** Not reported
Comparator	Following a 1-week run-in period where participants received placebo ICS and theophylline, those allocated to the comparator received a placebo inhaler, taken as two inhalations twice per day as well as two placebo capsules taken twice per day in addition to albuterol as-needed
Number of participants	SABA plus ICS: 177 allocated, 133 completed SABA: 87 allocated, 32 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Per protocol analysis with last observation carried forward from the last point before discontinuation due to protocol deviation or withdrawal

Study arms

SABA prn plus regular ICS (N = 177)
25 or 50 mcg fluticasone propionate, two inhalations twice per day plus SABA as-needed *Two study arms combined for this review*

SABA prn (N = 87)
Placebo inhaler, two inhalations twice per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 177)	SABA prn (N = 87)
% Female Sample size	n = 56 ; % = 32	n = 29 ; % = 33
Mean age (SD) Mean (range) Nominal	30	30
Mean age (SD) Mean (range) Range	12 to 75	12 to 64
Ethnicity (%) White Sample size	n = 161 ; % = 91	n = 75 ; % = 86
Comorbidities Nominal	NR	NR
Lung function (% of predicted) Mean FEV1	61	61

Characteristic	SABA prn plus regular ICS (N = 177)	SABA prn (N = 87)
Nominal		
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 177	SABA prn plus regular ICS, 12 week, N = 177	SABA prn, Baseline, N = 87	SABA prn, 12 week, N = 87
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-2.09 (2.99)	NA (NA)	-0.3 (2.52)

Reliever/rescue m–dication u–e - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 177	SABA prn plus regular ICS, 12 week, N = 177	SABA prn, Baseline, N = 87	SABA prn, 12 week, N = 87
Adverse events (potentially drug-related) Final values No of events	n = NA ; % = NA	n = 35 ; % = 20	n = NA ; % = NA	n = 10 ; % = 11

Adverse events (potentially –rug-relate–) - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use—- Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to regular treatment not monitored, 38% dropout rate, 38% difference in dropout rates between arms and reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events (potentially drug-related) —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported, adherence to regular treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Hoshino, 1998

Bibliographic Reference	Hoshino, M.; Nakamura, Y.; Sim, J. J.; Yamashiro, Y.; Uchida, K.; Hosaka, K.; Isogai, S.; Inhaled corticosteroid reduced lamina reticularis of the basement membrane by modulation of insulin-like growth factor (IGF)-I expression in bronchial asthma; Clinical & Experimental Allergy; 1998; vol. 28 (no. 5); 568-77

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)

Study location	Japan
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Schering-Plough Foundation
Inclusion criteria	Asthma according to ATS criteria Documented reversible airflow obstruction (≥20% increase in PEF or FEV1, either spontaneously or in response to SABA) and methacholine airway responsiveness
Exclusion criteria	Received inhaled or oral corticosteroids, or any other anti-inflammatory drugs in the past 4 months Smokers Respiratory tract infection within 2 weeks
Recruitment / selection of participants	Volunteers
Intervention(s)	Participants allocated to the intervention received 400 mcg beclomethasone dipropionate, one inhalation twice per day
Population subgroups	**Treatment status** Not reported

	Asthma history Not reported
Comparator	Participants allocated to the comparator received a matching placebo, one inhalation twice per day
Number of participants	SABA plus ICS: 15 allocated, 12 completed SABA: 15 allocated, 12 completed
Duration of follow-up	6 months
Indirectness	None
Additional comments	Per protocol analysis, including only 24 participants who completed both visits

Study arms

SABA prn plus regular ICS (N = 12)
400 mcg beclomethasone dipropionate, one inhalation twice per day plus salbutamol as-needed

SABA prn (N = 12)
Placebo twice per day plus salbutamol as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 12)	SABA prn (N = 12)
% Female Sample size	n = 3 ; % = 25	n = 2 ; % = 17
Mean age (SD) Mean (range) Nominal	29	27
Mean age (SD) Mean (range) Range	16 to 44	17 to 48
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) Mean (range) FEV1 Nominal	65.6	70.6
Lung function (% of predicted) Mean (range) FEV1 Range	55 to 85.6	57.1 to 80.5

Characteristic	SABA prn plus regular ICS (N = 12)	SABA prn (N = 12)
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 12	SABA prn plus regular ICS, 6 month, N = 12	SABA prn, Baseline, N = 12	SABA prn, 6 month, N = 12
Reliever/rescue medication use (Puffs per day) Final values Mean (SD)	5 (2.2)	2.4 (1.4)	5.1 (1.7)	5.8 (1.6)
Lung Function (FEV1) (% of predicted) Final values Mean (SD)	65.6 (9.1)	73.7 (10.1)	70.6 (7.2)	68.5 (9.2)

Outcome	SABA prn plus regular ICS, Baseline, N = 12	SABA prn plus regular ICS, 6 month, N = 12	SABA prn, Baseline, N = 12	SABA prn, 6 month, N = 12
Lung function (PEF) (Litres per minute) Final values Mean (SD)	409.1 (94.4)	505 (95.6)	457.4 (68.5)	436.7 (77.1)

Reliever/rescue m–dication u–e - Polarity - Lower values are better
Lung Fu–ction (FEV–) - Polarity - Higher values are better
Lung f–nction (PE–) - Polarity - Higher values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use— Mean (SD) - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to regular treatment not reported and 13% dropout rate with reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to regular treatment not reported and 13% dropout rate with reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to regular treatment not reported and 13% dropout rate with reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Jones, 1994

Bibliographic Reference	Jones, A. H.; Langdon, C. G.; Lee, P. S.; Lingham, S. A.; Nankani, J. P.; Follows, R. M.; Tollemar, U.; Richardson, P. D.; Pulmicort Turbohaler once daily as initial prophylactic therapy for asthma; Respiratory Medicine; 1994; vol. 88 (no. 4); 293-9

Study details

Secondary publication of	No additional information

another included study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	General practice
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Aged 12-70 years Mild to moderate stable asthma Documented response to β-agonist Peak expiratory flow rate (PEFR) ≥60% predicted at screening ≥2 days with asthma symptoms and β-agonist use during 5 day run-in
Exclusion criteria	Long-term oral glucocorticosteroids in past 6 months Short courses of oral glucocorticoids in past 2 months (except nasal steroids) Asthma exacerbation in past 2 months

	Cromoglycate or nedocromil use in past 2 months Respiratory infection or need for nebulised beta-2-agonist within 6 weeks Concomitant respiratory illness, symptomatic allergy or suspected seasonal allergy
Recruitment / selection of participants	No additional information
Intervention(s)	Following a one-week run-in, participants were allocated to one of three intervention regimens: • 400 mcg budesonide once per day in the morning • 400 mcg budesonide once per day in the evening • 200 mcg budesonide twice per day, once in the morning and once in the evening As-needed SABA was provided for use as-needed *Three study arms combined for this review*
Population subgroups	**Treatment status** Receiving SABA **Asthma history** Mixed

Comparator	Following a one-week run-in, participants allocated to the comparator received a placebo inhaler, taken twice per day with SABA provided to be used as-needed
Number of participants	SABA plus ICS: 255 allocated, 202 completed SABA: 85 allocated, 62 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat with last observation carried forward

Study arms

SABA prn plus regular ICS (N = 255)
400 mcg budesonide once per day in either the morning or evening, or 200 mcg twice per day plus SABA as-needed *Three study arms combined for this review*

SABA prn (N = 85)
Placebo inhaler taken twice per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 255)	SABA prn (N = 85)
% Female Sample size	n = 128 ; % = 50	n = 35 ; % = 41
Mean age (SD) Mean Nominal	36	40
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (L/min) PEF Mean (SD)	377 (99)	386 (99)
Asthma control (Puffs per day) Daytime SABA use Mean (SD)	3.37 (2.95)	3.33 (2.61)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 255	SABA prn plus regular ICS, 12 week, N = 255	SABA prn, Baseline, N = 85	SABA prn, 12 week, N = 85
Reliever/rescue medication use (daytime SABA use) (Puffs per day) Change scores Mean (SD)	NA (NA)	-1.14 (2.26)	NA (NA)	-0.59 (1.94)
Reliever/rescue medication use (nighttime SABA use) (Puffs per night) Change scores Mean (SD)	NA (NA)	-0.28 (1.28)	NA (NA)	0.13 (1.75)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	28 (49)	NA (NA)	6 (46)

Reliever/rescue medication use (dayt–me SABA us–) - Polarity - Lower values are better
Reliever/rescue medication use (nightt–me SABA us–) - Polarity - Lower values are better
Lung f–nction (PE–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 255	SABA prn plus regular ICS, 12 week, N = 255	SABA prn, Baseline, N = 85	SABA prn, 12 week, N = 85
Adverse events Final values No of events	n = NA ; % = NA	n = 70 ; % = 29	n = NA ; % = NA	n = 17 ; % = 23
Pneumonia (respiratory infections) Final values No of events	n = NA ; % = NA	n = 28 ; % = 11	n = NA ; % = NA	n = 17 ; % = 20

A–verse even–s - Polarity - Lower values are better
Pneumonia (respirator– infection–) - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use (daytime SABA use)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% missing outcome data with no information on dropout rates per study arm and reasons for discontinuation potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Reliever/rescue medication use (night time SABA use)—- Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% missing outcome data with no information on dropout rates per study arm and reasons for discontinuation potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF)—- Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% missing outcome data with no information on dropout rates per study arm and reasons for discontinuation potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – A–verse events –-No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneumonia (respiratory infections) —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable

Kemp, 2000

Bibliographic Reference	Kemp, J. P.; Berkowitz, R. B.; Miller, S. D.; Murray, J. J.; Nolop, K.; Harrison, J. E.; Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma; Journal of Allergy & Clinical Immunology; 2000; vol. 106 (no. 3); 485-92

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA

Study setting	No additional information
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Adults and adolescents with an asthma history of at least 6 months Using SABA for symptom relief for at least 2 weeks FEV1 55-85% of predicted FEV1 reversibility ≥12% and 200 mL after receiving SABA
Exclusion criteria	Received ICS within 3 months Received more than 14 days exposure to oral corticosteroids within 6 months Required daily nebulised beta-2-adrenergic agonists Required >12 inhalations of SABA on any two consecutive days Hospitalised for asthma within 3 months Received ventilatory support for asthma within 5 years Evidence of other respiratory diseases Smoked in the past 6 months

Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention received one of three medication regimens: • 100 mcg mometasone furoate, two inhalations in the morning (200 mcg) • 200 mcg mometasone furoate, two inhalations in the morning (400 mcg) • 100 mcg mometasone furoate, two inhalations in the morning and two in the evening (400 mcg) Placebo inhalers were given for use in the evening in the morning-dosing groups. SABA was provided for use as-needed *Three study arms combined for this review*
Population subgroups	**Treatment status** Receiving SABA **Asthma history** Not reported
Comparator	Participants allocated to the comparator received a placebo inhaler which was taken as two inhalations twice per day along with SABA as-needed
Number of participants	SABA plus ICS: 232 allocated, 207 completed SABA: 74 allocated, 56 completed

Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat with last observation carried forward

Study arms

SABA prn plus regular ICS (N = 232)
100 or 200 mcg mometasone furoate, two inhalations in the morning (200 or 400 mcg) or 100 mcg as two inhalations twice per day (400 mcg) plus SABA as-needed *Three study arms combined for this review*

SABA prn (N = 74)
Placebo inhaler taken as two inhalations twice per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 232)	SABA prn (N = 74)
% Female Sample size	n = 123 ; % = 53	n = 31 ; % = 42
Mean age (SD) Mean (SD)	30 (12)	32 (15)

Characteristic	SABA prn plus regular ICS (N = 232)	SABA prn (N = 74)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 185 ; % = 80	n = 63 ; % = 85
Black Sample size	n = 24 ; % = 10	n = 3 ; % = 4
Other Sample size	n = 23 ; % = 10	n = 8 ; % = 11
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	72 (9)	71 (9)
Asthma control (Puffs per day) Mean daily SABA use Nominal	3.73	4.5

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 232	SABA prn plus regular ICS, 12 week, N = 230	SABA prn, Baseline, N = 74	SABA prn, 12 week, N = 74
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.36 (0.5)	NA (NA)	0.14 (0.52)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	47 (63)	NA (NA)	23 (60)

Lung Fu–ction (FEV–) - Polarity - Higher values are better
Lung f–nction (PE–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 232	SABA prn plus regular ICS, 12 week, N = 232	SABA prn, Baseline, N = 74	SABA prn, 12 week, N = 74
Adverse events Final values No of events	n = NA ; % = NA	n = 53 ; % = 23	n = NA ; % = NA	n = 14 ; % = 19

A–verse even–s - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes – Lung Function (FEV1)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(14% dropout rate with reasons for discontinuation potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(14% dropout rate with reasons for discontinuation potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kerwin, 2008

Bibliographic Reference	Kerwin, E. M.; Nathan, R. A.; Meltzer, E. O.; Ortega, H. G.; Yancey, S. W.; Schoaf, L.; Dorinsky, P. M.; Efficacy and safety of fluticasone propionate/salmeterol 250/50 mcg Diskus administered once daily; Respiratory Medicine; 2008; vol. 102 (no. 4); 495-504

Study details

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA and Canada
Study setting	Outpatient clinics
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age Medical history of asthma requiring asthma therapy for at least 3 months Using SABA as monotherapy for at least one-month FEV1 50-85% of predicted and ≥12% reversibility after receiving SABA Symptom score ≥2 or used albuterol on ≥4 days of the second week of the run-in Evening PEF 50-90% of predicted and FEV1 within 15% of screening value
Exclusion criteria	History of life-threatening asthma

	Smoking within the previous year or a pack history >10 pack years Respiratory tract infection within 2 weeks History of significant concurrent disease Use of prophylactic SABA >2 times per day on >5 days a week
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 2-week run-in period, participants allocated to the intervention received 150 mcg fluticasone propionate, taken once daily in addition to albuterol as-needed *Study also contained two study arms including regular ICS/LABA–combinations - excluded from this review due to not containing relevant interventions*
Population subgroups	**Treatment status** Receiving SABA **Asthma history** Not reported
Comparator	Following a 2-week run-in period, participants allocated to the comparator received a placebo inhaler, taken once daily in addition to albuterol as-needed

Number of participants	SABA plus ICS: 212 allocated, 182 completed SABA: 212 allocated, 163 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat with last observation carried forward for FEV1 and average score over the treated period for all other outcomes

Study arms

SABA prn plus regular ICS (N = 212)
250 mcg fluticasone propionate once per day plus SABA as-needed

SABA prn (N = 212)
Placebo inhaler once per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	**SABA prn plus regular ICS (N = 212)**	**SABA prn (N = 212)**
% Female Sample size	n = 112 ; % = 53	n = 110 ; % = 52

Characteristic	SABA prn plus regular ICS (N = 212)	SABA prn (N = 212)
Mean age (SD) Mean (range) Nominal	31.7	33
Mean age (SD) Mean (range) Range	12 to 85	12 to 73
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 167 ; % = 79	n = 160 ; % = 75
African-American Sample size	n = 26 ; % = 12	n = 29 ; % = 14
Asian Sample size	n = 2 ; % = 1	n = 4 ; % = 2
Hispanic Sample size	n = 16 ; % = 8	n = 16 ; % = 8
Other Sample size	n = 1 ; % = 0	n = 3 ; % = 1
Comorbidities	NR	NR

Characteristic	SABA prn plus regular ICS (N = 212)	SABA prn (N = 212)
Nominal		
Lung function (% of predicted) FEV1 Mean (SD)	74.5 (10.5)	73.2 (10.8)
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 212	SABA prn plus regular ICS, 12 week, N = 212	SABA prn, Baseline, N = 212	SABA prn, 12 week, N = 212
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-1.5 (2.8)	NA (NA)	-0.4 (2.2)

Outcome	SABA prn plus regular ICS, Baseline, N = 212	SABA prn plus regular ICS, 12 week, N = 212	SABA prn, Baseline, N = 212	SABA prn, 12 week, N = 212
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.36 (0.44)	NA (NA)	0.18 (0.44)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	33.6 (43.7)	NA (NA)	12.6 (43.7)

Reliever/rescue m–dication u–e - Polarity - Lower values are better
Lung Fu–ction (FEV–) - Polarity - Higher values are better
Lung f–nction (PE–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 212	SABA prn plus regular ICS, 12 week, N = 212	SABA prn, Baseline, N = 212	SABA prn, 12 week, N = 212
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 2 ; % = 1	n = NA ; % = NA	n = 12 ; % = 6
Adverse events Final values No of events	n = NA ; % = NA	n = 112 ; % = 53	n = NA ; % = NA	n = 110 ; % = 52

Severe asthma –xacerbatio–s - Polarity - Lower values are better
A–verse even–s - Polarity - Lower values are better

Severe asthma exacerbations defined as need for medication other than randomised treatment or rescue albuterol which led to study withdrawal

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use—- Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 19% missing data, 9% difference in dropout rate between arms and reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1)—- Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 19% missing data, 9% difference in dropout rate between arms and reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 19% missing data, 9% difference in dropout rate between arms and reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Nathan, 1999

Bibliographic Reference	Nathan, R. A.; Pinnas, J. L.; Schwartz, H. J.; Grossman, J.; Yancey, S. W.; Emmett, A. H.; Rickard, K. A.; A six-month, placebo-controlled comparison of the safety and efficacy of salmeterol or beclomethasone for persistent asthma; Annals of Allergy, Asthma, & Immunology; 1999; vol. 82 (no. 6); 521-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by Glaxo Wellcome
Inclusion criteria	Aged ≥12 years

	Non-smoking Diagnosed with asthma for ≥3 months FEV1 65-90% of predicted and ≥12% increase after receiving SABA Receiving as-needed SABA
Exclusion criteria	Used inhaled or oral corticosteroids within the last 6 months Decline in FEV1 ≥15% after saline inhalation Hospital admission due to asthma within 30 days >12 puffs of albuterol on 3 of any 7 days of the screening period
Recruitment / selection of participants	Recruited from 25 centres in USA
Intervention(s)	Participants allocated to the intervention received 84 mcg beclomethasone dipropionate four times per day, plus albuterol as-needed *Study also included an arm where participants received LABA –wice per day - excluded from this review due to not containing a relevant intervention*
Population subgroups	**Treatment status** Receiving SABA

	Asthma history Not reported
Comparator	Participants allocated to the intervention received a placebo inhaler plus albuterol as-needed
Number of participants	SABA plus ICS: 129 allocated, 106 completed SABA: 129 allocated. 101 completed
Duration of follow-up	6 months
Indirectness	Downgraded by one increment due to population–indirectness - participants could have been receiving intranasal corticosteroids or intranasal cromolyn sodium at screening and were allowed to maintain this treatment at a constant dose (number of participants receiving concomitant treatment not reported)
Additional comments	Intention to treat (minus four participants given incor–ect inhaler) - method of imputation of missing data reported

Study arms

SABA prn plus regular ICS (N = 129)
84 mcg beclomethasone dipropionate four times per day plus SABA as-needed

SABA prn (N = 129)
Placebo inhaler plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 129)	SABA prn (N = 129)
% Female Sample size	n = 73 ; % = 57	n = 65 ; % = 50
Mean age (SD) Mean (SE)	29.9 (1.1)	29.1 (1.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (Litres) FEV1 Mean (SE)	2.78 (0.06)	2.88 (0.06)
Asthma control Number hospitalised within 12 months Sample size	n = 0 ; % = 0	n = 0 ; % = 0

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 129	SABA prn plus regular ICS, 6 month, N = 129	SABA prn, Baseline, N = 129	SABA prn, 6 month, N = 129
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.23 (0.45)	NA (NA)	0.08 (0.45)

Lung Fu–ction (FEV–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 129	SABA prn plus regular ICS, 6 month, N = 129	SABA prn, Baseline, N = 129	SABA prn, 6 month, N = 129
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 13 ; % = 10	n = NA ; % = NA	n = 17 ; % = 13

Severe asthma –xacerbatio–s - Polarity - Lower values are better

Contrast Outcomes

Outcome	SABA prn plus regular ICS vs SABA prn, Baseline, N2 = 129, N1 = 129	SABA prn plus regular ICS vs SABA prn, 6 month, N2 = 129, N1 = 129
Reliever/rescue medication use (SABA-free nights) (%) Change scores Mean (p value)	NA (NA)	14 (0.014)

Reliever/rescue medication use (SABA–free night–) - Polarity - Higher values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes – Lung Function (FEV1)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to maintenance therapy not reported, 20% dropout rate with reasons for discontinuation potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations —No Of Events - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method and adherence to maintenance therapy not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Cont–ast Outcomes - Reliever/rescue medication use (SABA-free nights) —Mean P Value - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to maintenance therapy not reported, 20% dropout rate with reasons for discontinuation potentially related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Nayak, 2002

Bibliographic Reference	Nayak, A.; Lanier, R.; Weinstein, S.; Stampone, P.; Welch, M.; Efficacy and safety of beclomethasone dipropionate extrafine aerosol in childhood asthma: a 12-week, randomized, double-blind, placebo-controlled study; Chest; 2002; vol. 122 (no. 6); 1956-65

Study details

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Hospital outpatient department
Study dates	No additional information
Sources of funding	Sponsored by 3M Pharmaceuticals
Inclusion criteria	5-12 years of age Stable, moderate, symptomatic asthma for at least 6 months Receiving SABA on an as-needed basis FEV1 50-80% of predicted FEV1 increase ≥12% after receiving SABA Use of beta-agonist therapy on at least 50% of days during a 2-week run-in
Exclusion criteria	Any significant, non-reversible pulmonary disease other than asthma

	Significant immunologic, neoplastic, endocrine, haematological, cardiac, hepatic, renal, GI, neurologic or psychiatric abnormalities or illness Respiratory tract infection within 4 weeks Use of injectable corticosteroids within 6 months, oral corticosteroids within 8 weeks or inhaled corticosteroids within 6 weeks Use of any other maintenance medications
Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention arms received one of two interventions: • 40 mcg beclomethasone dipropionate, one inhalation twice per day (80 mcg) • 80 mcg beclomethasone dipropionate, one inhalation twice per day (160 mcg) Pirbuterol was provided to be used as-needed *Two study arms combined for this review*
Population subgroups	**Treatment status** Receiving SABA

	Asthma history Not reported
Comparator	Participants allocated to the comparator received a placebo inhaler, taken as one inhalation twice per day plus pirbuterol as-needed
Number of participants	SABA plus ICS: 237 allocated, 213 completed SABA: 116 allocated, 97 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat, method of imputation not reported

Study arms

SABA prn plus regular ICS (N = 237)
40 or 80 mcg beclomethasone dipropionate, one inhalation twice per day plus SABA as-needed

SABA prn (N = 116)
Placebo inhaler, one inhalation twice per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 237)	SABA prn (N = 116)
% Female Sample size	n = 90 ; % = 38	n = 39 ; % = 34
Mean age (SD) Mean (SD)	9.2 (2)	9.3 (2.1)
Ethnicity (%) White Sample size	n = 180 ; % = 76	n = 94 ; % = 81
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	72.1 (7.5)	71 (7.8)
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 237	SABA prn plus regular ICS, 12 week, N = 237	SABA prn, Baseline, N = 116	SABA prn, 12 week, N = 116
Adverse events Final values No of events	n = NA ; % = NA	n = 167 ; % = 70	n = NA ; % = NA	n = 82 ; % = 71
Adrenal insufficiency (abnormal response to low-dose ACTH stimulation) Final values. SABA plus ICS n=41, SABA n=20 No of events	n = 2 ; % = 5	n = 1 ; % = 2	n = 3 ; % = 15	n = 3 ; % = 15

A–verse even–s - Polarity - Lower values are better
Adrenal insufficiency (abnormal response to low-dose ACTH–stimulatio–) - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Adverse events —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichoto–ous Outcomes - Adrenal insufficiency —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Subgroup analysis of participants who were willing to have blood tests with complete-case analysis used only including those with pre and post study measurements and no indication of dropout rates in the subgroup)*
Overall bias and Directness	Overall Directness	Directly a’plicable

O'Byrne, 2014

Bibliograph’c Reference	O'Byrne, P. M.; Woodcock, A.; Bleecker, E. R.; Bateman, E. D.; Lotvall, J.; Forth, R.; Medley, H.; Jacques, L.; Busse, W. W.; Efficacy and safety of once-daily fluticasone furoate 50 mcg in adults with persistent asthma: a 12-week randomized trial; Respiratory Research; 2014; vol. 15; 88

Study details

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01436071
Study type	Randomised controlled trial (RCT)
Study location	Mexico, Peru, Russia, USA
Study setting	No additional information
Study dates	S–ptember 2011 - August 2012
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	Aged ≥12 years Diagnosis of asthma for ≥12 weeks Receiving treatment with SABA with or without an LTRA FEV1 ≥60% of predicted and ≥12% and 200 mL reversibility Required SABA and/or had diary-recorded symptoms on ≥4 of the last 7 consecutive days of the run-in period
Exclusion criteria	Received ICS or LABA within 4 weeks Presence of oral/oropharyngeal candidiasis

Recruitment / selection of participants	Recruited from 19 centres, method not reported
Intervention(s)	Participants allocated to the intervention arm received 50 mcg fluticasone furoate, one inhalation once per day in the evening, plus salbutamol as-needed
Population subgroups	**Treatment status** Receiving SABA **Asthma history** Not reported
Comparator	Participants allocated to the comparator arm received a placebo inhaler which was taken as one inhalation once per day in the evening, plus salbutamol as-needed
Number of participants	SABA plus ICS: 111 allocated, 100 completed SABA: 111 allocated, 90 completed
Duration of follow-up	12 weeks
Indirectness	Downgraded by one increment due to population–indirectness - participants could have been treated with SABA, LTRAs or a combination prior to screening (number of participants this applied to not reported)
Additional comments	Intention to treat and per protocol

Study arms

SABA prn plus regular ICS (N = 111)
50 mcg fluticasone furoate, one inhalation once daily plus SABA as-needed

SABA prn (N = 111)
Placebo inhaler, one inhalation once daily plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 111)	SABA prn (N = 111)
% Female Sample size	n = 63 ; % = 57	n = 70 ; % = 63
Mean age (SD) Mean (SD)	36.7 (16.2)	33.8 (13.9)
Ethnicity Sample size	n = 63 ; % = 57	n = 70 ; % = 63
American Indian or Alaska Native Sample size	n = 45 ; % = 41	n = 59 ; % = 53
White Sample size	n = 42 ; % = 38	n = 29 ; % = 26
American Indian or Alaska Native and White Sample size	n = 24 ; % = 22	n = 21 ; % = 19

Characteristic	SABA prn plus regular ICS (N = 111)	SABA prn (N = 111)
Other Sample size	n = 0 ; % = 0	n = 2 ; % = 2
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	74.71 (9.49)	77.33 (12.88)
Asthma control (%) SABA-free days Mean (SD)	10.2 (21.5)	7.5 (21)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 111	SABA prn plus regular ICS, 12 week, N = 111	SABA prn, Baseline, N = 111	SABA prn, 12 week, N = 110
Quality of life (Asthma Quality of Life Questionnaire) Scale range: 1-7, change scores (SABA plus ICS n=100, SABA n=92) Mean (SD)	NA (NA)	1.3 (0.93)	NA (NA)	0.84 (0.93)
Asthma Control (Asthma Control Test) Scale range: 5-25, change scores (SABA plus ICS n=100, SABA n=92) Mean (SD)	NA (NA)	6.2 (3.8)	NA (NA)	4 (3.7)
Reliever/rescue medication use (SABA-free days) (%) Change scores (average over weeks 1-12) Mean (SD)	NA (NA)	28.7 (29.2)	NA (NA)	17.1 (29.2)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.16 (0.34)	NA (NA)	0.04 (0.34)
Lung function (PEF) (Litres per minute) Change scores (average over weeks 1-12) Mean (SD)	NA (NA)	34.5 (38.3)	NA (NA)	22.9 (38.3)

Quality of life (Asthma Quality of Life Q–estionnair–) - Polarity - Higher values are better
Asthma Control (Asthma –ontrol Tes–) - Polarity - Higher values are better
Reliever/rescue medication use (SA–A-free day–) - Polarity - Higher values are better
Lung Fu–ction (FEV–) - Polarity - Higher values are better

Lung f–nction (PE–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 121	SABA prn plus regular ICS, 12 week, N = 121	SABA prn, Baseline, N = 121	SABA prn, 12 week, N = 121
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 3 ; % = 3
Adverse events Final values No of events	n = NA ; % = NA	n = 37 ; % = 31	n = NA ; % = NA	n = 46 ; % = 38
Pneumonia Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Severe asthma –xacerbatio–s - Polarity - Lower values are better
A–verse even–s - Polarity - Lower values are bet–er
Pneumon–a - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes – Quality of life (Asthma Quality of Life Questionnaire)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(14% missing outcome data, 7% difference between dropout rates per study arm and reasons for discontinuation that could have been related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Asthma Control (Asthma Control Test)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(14% missing outcome data, 7% difference between dropout rates per study arm and reasons for discontinuation that could have been related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Reliever/rescue medication use (SABA-freedays) – Mean (SD) -SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(14% missing outcome data, 7% difference between dropout rates per study arm and reasons for discontinuation that could have been related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(14% missing outcome data, 7% difference between dropout rates per study arm and reasons for discontinuation that could have been related 'o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(14% missing outcome data, 7% difference between dropout rates per study arm and reasons for discontinuation that could have been related 'o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneumonia —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Papi, 2009

Bibliographic Reference	Papi, A.; Nicolini, G.; Baraldi, E.; Boner, A. L.; Cutrera, R.; Rossi, G. A.; Fabbri, L. M.; Beclomethasone; Salbutamol Treatment for Children Study, Group; Regular vs prn nebulized treatment in wheeze preschool children; Allergy; 2009; vol. 64 (no. 10); 1463-1471

Study details

Secondary publication of another included study- see primary study for details	No additional information

Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	Paediatric specialist care units
Study dat–s	March 2006 - January 2007
Sources of funding	Funded by Chiesi Farmaceutici SpA
Inclusion criteria	Aged 1-4 years Frequent wheezing (≥3 episodes in the past 6 months) and referred to the specialist unit due to a further episode
Exclusion criteria	History of severe exacerbations requiring systemic glucocorticoids Chest infection or hospitalisation within 4 weeks
Recruitment / selection of participants	Recruited from 19 specialist paediatric units, method not reported
Intervention(s)	Participants were allocated to one of three treatment options: – • Regular ICS - 400 mcg beclomethasone, taken twice daily, plus 2500 mcg salbutamol as-needed for symptom relief • ICS/S–BA as-needed - placebo taken twice daily plus 800 mcg beclomethasone 1600 mcg salbutamol as-needed

	• S–BA as-needed - placebo taken twice daily plus 2500 mcg salbutamol as-needed
Population subgroups	**Treatment status** Not reported **Asthma history** No previous exacerbations
Comparator	See interventions
Number of participants	276 randomised 110 allocated to ICS, 108 completed 110 allocated to ICS/SABA, 106 completed 56 allocated to SABA, 53 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat with last observation carried forward

Study arms

SABA prn plus regular ICS (N = 110)
400 mcg beclomethasone, one inhalation twice per day, plus salbutamol as-needed

ICS combination inhaler prn (N = 110)

800/1600 mcg beclomethasone/salbutamol, taken as-needed

SABA prn (N = 56)
2500 mcg salbutamol taken as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 110)	ICS combination inhaler prn (N = 110)	SABA prn (N = 56)
% Female Sample size	n = 46 ; % = 42	n = 42 ; % = 38	n = 22 ; % = 39
Mean age (SD) Mean (SD)	2.35 (0.81)	2.26 (0.79)	2.29 (0.78)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR

Characteristic	SABA prn plus regular ICS (N = 110)	ICS combination inhaler prn (N = 110)	SABA prn (N = 56)
Asthma control (Puffs per day) Daytime SABA use Mean (SD)	0.35 (0.41)	0.26 (0.29)	0.25 (0.25)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 110	SABA prn plus regular ICS, 12 week, N = 110	ICS combination inhaler prn, Baseline, N = 110	ICS combination inhaler prn, 12 week, N = 110	SABA prn, Baseline, N = 56	SABA prn, 12 week, N = 56
Adverse events Final values No of events	n = NA ; % = NA	n = 22 ; % = 20	n = NA ; % = NA	n = 30 ; % = 27	n = NA ; % = NA	n = 17 ; % = 30

A–verse even–s - Polarity - Lower values are better

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 110	SABA prn plus regular ICS, 12 week, N = 108	ICS combination inhaler prn, Baseline, N = 110	ICS combination inhaler prn, 12 week, N = 106	SABA prn, Baseline, N = 56	SABA prn, 12 week, N = 53
Reliever/rescue medication use (daytime SABA use) (Puffs per day) Change scores Mean (SD)	NA (NA)	-0.24 (0.44)	NA (NA)	-0.17 (0.38)	NA (NA)	-0.09 (0.42)
Reliever/rescue medication use (nighttime SABA use) (Puffs per night) Change scores Mean (SD)	NA (NA)	-0.1 (0.21)	NA (NA)	-0.12 (0.2)	NA (NA)	-0.08 (0.25)
Adrenal insufficiency (salivary cortisol) (µg/100 mL) Change scores Mean (SD)	NA (NA)	-1.92 (7.39)	NA (NA)	0.6 (27.18)	NA (NA)	0.55 (3.2)

Reliever/rescue medication use (dayt–me SABA us–) - Polarity - Lower values are better
Reliever/rescue medication use (nightt–me SABA us–) - Polarity - Lower values are better
Adrenal insufficiency (saliv–ry cortiso–) - Polarity - Higher values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Adverse events —No Of Events - SABA prn plus regular ICS-ICS combination inhaler prn-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(daytimeSABAuse)-MeanSD-SABA prn plus regular ICS-ICS combination inhaler prn-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Reliever/rescue medication use (night time SABA use)— Mean (SD) - SABA prn plus regular ICS-ICS combination inhaler prn-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Adrenalin sufficiency (salivary cortisol)— Mean (SD) - SABA prn plus regular ICS-ICS combination inhaler prn-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Ruff, 2003

Bibliographic Reference	Ruff, M. E.; Szefler, S. J.; Meltzer, E. O.; Berger, W. E.; Efficacy and safety of extrafine beclomethasone dipropionate aerosol therapy in children with asthma: A twelve-week placebo-controlled trial; Pediatric Asthma, Allergy and Immunology; 2003; vol. 16 (no. 1); 1-13

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by 3M Pharmaceuticals
Inclusion criteria	Children aged 6-12 years Mild to moderate symptomatic asthma for at least 6 months Steroid naïve, receiving only SABA as-needed FEV1 50-85% of predicted FEV1 reversibility ≥12% after receiving SABA Able to appropriately use an inhaler and peak flow monitor
Exclusion criteria	Any significant non-reversible pulmonary disease Evidence of any clinically significant immunologic, neoplastic, endocrine, hematologic, cardiac, hepatic, renal, gastrointestinal, neurologic, or psychiatric abnormalities Upper respiratory tract infection with associated symptoms that affected asthma control within 2 weeks or a lower respiratory tract infection (e.g., bronchitis, pneumonia) within 4 weeks Use of systemic or inhaled corticosteroids within 6 months and 6 weeks, respectively Use of more than 200 mg/d of a nasal steroid Visible oropharyngeal candidiasis within 2 weeks

Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention arms received either 50 or 100 mcg fluticasone propionate, both one inhalation twice per day plus SABA as-needed for symptom relief *Two study arms containing two ICS dose combined for this review*
Population subgroups	**Previous treatment** All receiving SABA **Asthma history** Not reported
Comparator	Participants allocated to the comparator received a placebo inhaler, taken as one inhalation twice per day, plus SABA as-needed for symptom relief
Number of participants	SABA plus ICS: 212 allocated, 180 completed SABA: 107 allocated, 83 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat and per protocol analysis

Study arms

SABA prn plus regular ICS (N = 212)
One inhalation twice per day 50 or 100 mcg fluticasone propionate plus SABA as-needed *Two study arms combined for this review*

SABA prn (N = 107)
One inhalation twice per day of placebo plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 212)	SABA prn (N = 107)
% Female Sample size	n = 81 ; % = 38	n = 47 ; % = 44
Mean age (SD) Mean (SD)	9.5 (1.8)	9.8 (1.8)
Ethnicity White Sample size	n = 169 ; % = 80	n = 84 ; % = 79
Comorbidities Nominal	NR	NR

Characteristic	SABA prn plus regular ICS (N = 212)	SABA prn (N = 107)
Lung function (% of predicted) FEV1 Mean (SD)	73.9 (9.1)	74.1 (9.5)
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 205	SABA prn plus regular ICS, 12 week, N = 205	SABA prn, Baseline, N = 104	SABA prn, 12 week, N = 104
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	19.8 (39.6)	NA (NA)	5.5 (40.3)

Lung f–nction (PE–) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 212	SABA prn plus regular ICS, 12 week, N = 212	SABA prn, Baseline, N = 107	SABA prn, 12 week, N = 107
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 28 ; % = 13	n = NA ; % = NA	n = 20 ; % = 19
Adverse events Final values No of events	n = NA ; % = NA	n = 121 ; % = 57	n = NA ; % = NA	n = 73 ; % = 68
Pneumonia Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 1

Severe asthma –xacerbatio–s - Polarity - Lower values are better
A–verse even–s - Polarity - Lower values are bet–er
Pneumon–a - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes – Lung function (PEF)—– Mean (SD) - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 62.5% adherence to study medications, 17.6% missing outcome data, ~7% difference in missing data between study arms and reasons for discontinuation that could be related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma –xacerbations –—No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and 62.5% adherence to study medications)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events —–No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and 62.5% adherence to study medications)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneumonia —No Of Events - SABA prn plus regular ICS-SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and 62.5% adherence to study medications)*
Overall bias and Directness	Overall Directness	Directly applicable

Schokker, 2008

Bibliographic Reference	Schokker, S.; Kooi, E. M.; de Vries, T. W.; Brand, P. L.; Mulder, P. G.; Duiverman, E. J.; van der Molen, T.; Inhaled corticosteroids for recurrent respiratory symptoms in preschool children in general practice: randomized controlled trial; Pulmonary Pharmacology & Therapeutics; 2008; vol. 21 (no. 1); 88-97

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ASTERISK
Study type	Randomised controlled trial (RCT)

Study location	The Netherlands
Study setting	Primary care (general practice)
Study da–es	June 2001 - January 2003
Sources of funding	Sponsored by GlaxoSmithKline
Inclusion criteria	Children aged 1-5 years Presenting to GPs with recurrent respiratory symptoms (cough, wheeze and/or shortness of breath) in whom they considered prescribing ICS for asthma
Exclusion criteria	Treated with ICS within 4 weeks or during the run-in Received oral steroids within 8 weeks or during the run-in Symptoms on <7 out of 14 days of the run-in Other respiratory diseases Poorly controlled systemic diseases Inability to fill in diary or appropriately use medication
Recruitment / selection of participants	182 GPs provided eligible patient information to researchers for a screening visit
Intervention(s)	Participants allocated to the intervention received 50 mcg fluticasone propionate, one inhalation twice per day with a face mask or mouth piece according to the age and suitability of the device for each individual, along with salbutamol as-needed for symptom relief

Population subgroups	**Treatment status** Not reported **Asthma history** Not reported
Comparator	Participants allocated to the intervention received placebo, one inhalation twice per day with a face mask or mouth piece according to the age and suitability of the device for each individual, along with salbutamol as-needed for symptom relief
Number of participants	SABA plus ICS: 48 allocated, 45 completed SABA: 48 allocated, 43 completed
Duration of follow-up	6 months
Indirectness	Downgraded by one increment due to population–indirectness - 38% of participants had previously been treated with ICS
Additional comments	Intention to treat

Study arms

SABA prn plus regular ICS (N = 48)
50 mcg fluticasone propionate, one inhalation twice per day plus SABA as-needed

SABA prn (N = 48)
Placebo, one inhalation twice per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 48)	SABA prn (N = 48)
% Female Sample size	n = 15	n = 15
Mean age (SD) Mean (SD)	2.5 (1.2)	2.8 (1.2)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function Nominal	NR	NR
Asthma control (Puffs per day) Daytime SABA use Median (IQR)	0.21 (0 to 1.11)	0.37 (0.01 to 0.98)

Outcomes

Study timepoints

- Baseline

- 6 month

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 48	SABA prn plus regular ICS, 6 month, N = 48	SABA prn, Baseline, N = 48	SABA prn, 6 month, N = 48
Hospital admissions Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 2 ; % = 4
Adverse events Final values No of events	n = NA ; % = NA	n = 30 ; % = 63	n = NA ; % = NA	n = 29 ; % = 60

Hospit–l admissio–s - Polarity - Lower values are better
A–verse even–s - Polarity - Lower values are better

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 46	SABA prn plus regular ICS, 6 month, N = 46	SABA prn, Baseline, N = 46	SABA prn, 6 month, N = 46
Reliever/rescue medication use (daytime SABA use) (Puffs per day) Final values Mean (SD)	NA (NA)	0.37 (0.71)	NA (NA)	0.31 (0.5)

Outcome	SABA prn plus regular ICS, Baseline, N = 46	SABA prn plus regular ICS, 6 month, N = 46	SABA prn, Baseline, N = 46	SABA prn, 6 month, N = 46
Reliever/rescue medication use (night time SABA use) (Puffs per night) Final values Mean (SD)	NA (NA)	0.11 (0.3)	NA (NA)	0.06 (0.14)

Reliever/rescue medication use (dayt–me SABA us–) - Polarity - Lower values are better
Reliever/rescue medication use (night t–me SABA us–) - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Hospit–l admissions —No Of Events - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes Adverse events —No Of Events - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Reliever/rescue medication use (daytime SABA use)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Reliever/rescue medication use (nighttime SABA use)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Sheffer, 1996

Bibliographic Reference	Sheffer, A. L.; LaForce, C.; Chervinsky, P.; Pearlman, D.; Schaberg, A.; Fluticasone propionate aerosol: Efficacy in patients with mild to moderate asthma; Journal of Family Practice; 1996; vol. 42 (no. 4); 369-375

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with	No additional information

this study included in review	
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by Glaxo-Wellcome
Inclusion criteria	≥12 years of age History of asthma requiring daily pharmacotherapy for at least 3 months FEV1 45-75% of predicted at screening and 45-65% after run-in or 65-75% in addition to one or more of: ≥1 day on which >8 albuterol inhalations were used, ≥20% evening-morning peak flow variability on ≥2 days, total weekly score ≥7 on any asthma symptom (cough, wheeze or shortness of breath), ≥2 nights with awakening and albuterol use ≥15% increase in FEV1 after receiving SABA
Exclusion criteria	Pregnant or lactating Taken long-term oral steroids within the past 2 years (daily or every other day use) Used intranasal, injectable, oral, topical or inhaled corticosteroids or cromolyn sodium within 1-month History of life-threatening asthma

Recruitment / selection of participants	No additional information
Intervention(s)	Following a one-week run-in period, participants allocated to the intervention arms received one of: • 25 mcg fluticasone propionate, one inhalation of active (25 mcg) and one placebo twice per day plus albuterol as-needed • 50 mcg fluticasone propionate, one inhalation of active (50 mcg) and one placebo twice per day plus albuterol as-needed • 100 mcg fluticasone propionate, two inhalations of active (50 mcg) twice per day plus albuterol as-needed *Three study arms combined for this review*
Population subgroups	**Treatment status** Not reported **Asthma history** Not reported
Comparator	Following a one-week run-in period, participants allocated to the comparator arm received a placebo inhaler, two puffs twice per day, plus albuterol as-needed
Number of participants	SABA plus ICS: 234 allocated, 147 completed SABA: 73 allocated, 29 completed

Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Available case analysis

Study arms

SABA prn plus regular ICS (N = 234)
25, 50 or 100 mcg fluticasone propionate, one inhalation twice per day plus SABA as-needed *Three study arms combined for this review*

SABA prn (N = 73)
Placebo inhaler twice per day plus SABA as-needed

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 234)	SABA prn (N = 73)
% Female Sample size	n = 91 ; % = 39	n = 31 ; % = 42
Mean age (SD) Mean (range) Nominal	29	30

Characteristic	SABA prn plus regular ICS (N = 234)	SABA prn (N = 73)
Mean age (SD) Mean (range) Range	12 to 72	12 to 54
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 204 ; % = 87	n = 57 ; % = 78
Black Sample size	n = 18 ; % = 8	n = 9 ; % = 12
Hispanic Sample size	n = 8 ; % = 3	n = 6 ; % = 8
Other Sample size	n = 4 ; % = 2	n = 1 ; % = 1
Comorbidities Nominal	NR	NR
Lung function (% of predicted) Mean FEV1 Nominal	63	62
Asthma control	NR	NR

Characteristic	SABA prn plus regular ICS (N = 234)	SABA prn (N = 73)
Nominal		

Outcomes

Study timepoints

- Baseline
- End of treatment (Data was analysed as change from baseline, with the data presented as the last available measurement which varied between individuals)

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 234	SABA prn plus regular ICS, End of treatment , N = 234	SABA prn, Baseline, N = 73	SABA prn, End of treatment , N = 73
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-1.75 (3.16)	NA (NA)	-0.28 (2.48)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.44 (0.59)	NA (NA)	0.14 (0.51)
Lung function (PEF) (Litres per minute) Change scores	NA (NA)	34 (53)	NA (NA)	12 (42)

Outcome	SABA prn plus regular ICS, Baseline, N = 234	SABA prn plus regular ICS, End of treatment , N = 234	SABA prn, Baseline, N = 73	SABA prn, End of treatment , N = 73
Mean (SD)				

Reliever/rescue m–dication u–e - Polarity - Lower values are better
Lung Fu–ction (FEV–) - Polarity - Higher values are better
Lung f–nction (PE–) - Polarity - Higher values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use— Mean (SD) - SABA prn plus regular ICS-SABA prn-t End of treatment

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to treatment not monitored, 53% missing data in SABA prn arm and 25-37% missing in SABA+ICS arms with the majority discontinuing due to not achieving study-defined asthma control before the end of the trial)*
Overall bias and Directness	Overall Directness	Directly applicable

Contin–ous Outcomes - Lung Function (FEV1)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t End of treatment

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to treatment not monitored, 53% missing data in SABA prn*

Section	Question	Answer
		arm and 25-37% missing in SABA+ICS arms with the majority discontinuing due to not achieving study-defined asthma control before the end of the trial)
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung f–nction (PEF– - Mean (SD) - SABA prn plus regular ICS-SABA prn-t End of treatment

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to treatment not monitored, 53% missing data in SABA prn arm and 25-37% missing in SABA+ICS arms with the majority discontinuing due to not achieving study-defined asthma control before the end of the trial)*
Overall bias and Directness	Overall Directness	Directly applicable

Teper, 2004

Bibliographic Reference	Teper, A. M.; Colom, A. J.; Kofman, C. D.; Maffey, A. F.; Vidaurreta, S. M.; Bergada, I.; Effects of inhaled fluticasone propionate in children less than 2 years old with recurrent wheezing; Pediatric Pulmonology; 2004; vol. 37 (no. 2); 111-5

Study details

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Argentina
Study setting	Respiratory disease centre’at a children's hospital
Study dat–s	March 1999 - March 2000
Sources of funding	–one reported - inhalers provided by Glaxo Wellcome
Inclusion criteria	Aged <2 years Asthmatic symptoms (≥3 episodes of wheeze with clinical improvement after receiving bronchodilators) Familial history of asthma or any other clinical finding indicating atopy (allergic rhinitis or eczema) in first-degree relatives
Exclusion criteria	History of severe respiratory infection, cystic fibrosis, aspirative pathology, pulmonary or airways anomalies, bronchopulmonary dysplasia and congenital heart disease Previously received ICS or sodium cromoglycate
Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention arms received 50 or 125 mcg fluticasone propionate, one inhalation twice per day via a plastic holding chamber attached to a face mask, with albuterol taken as needed for symptom relief

	Two study arms containing 50 and 125 mcg FP combined for this review
Population subgroups	**Treatment status** Not reported **Asthma history** Not reported
Comparator	Participants allocated to the comparator arm received a placebo inhaler, taken as one inhalation twice per day via a plastic holding chamber attached to a face mask. with albuterol taken as needed for symptom relief
Number of participants	34 randomised 22 allocated to SABA plus ICS, 20 completed 14 allocated to SABA, 10 completed
Duration of follow-up	6 months
Indirectness	None
Additional comments	Complete case analysis

Study arms

SABA prn plus regular ICS (N = 20)
50 or 125 mcg fluticasone propionate, one inhalation twice per day *Two study arms combined for this review*

SABA prn (N = 10)
Placebo inhaler, one inhalation twice per day

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 20)	SABA prn (N = 10)
% Female Sample size	n = 7 ; % = 35	n = 5 ; % = 50
Mean age (SD) (Months) Mean (SD)	13.7 (5.5)	11.9 (6.4)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints
- Baseline
- 6 month

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 20	SABA prn plus regular ICS, 6 month, N = 20	SABA prn, Baseline, N = 10	SABA prn, 6 month, N = 10
Reliever/rescue medication use (number of days with SABA use) (days) Final values Mean (SD)	NA (NA)	7.8 (1.5)	NA (NA)	24.3 (1.3)

Reliever/rescue medication use (number of days w–th SABA us–) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 20	SABA prn plus regular ICS, 6 month, N = 20	SABA prn, Baseline, N = 10	SABA prn, 6 month, N = 10
Hospital admissions Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Hospit–l admissio–s - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use (number of days with SABA use)—- Mean (SD) - SABA prn plu– regular ICS - SABA prn

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence to treatment not monitored, 12% missing data with complete case analysis, and reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Hospital admissions —-No Of Events - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence to treatment not monitored, 12% missing data with complete case analysis, and reasons for discontinuation related ’o participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Teper, 2005

Bibliographic Reference	Teper, A. M.; Kofman, C. D.; Szulman, G. A.; Vidaurreta, S. M.; Maffey, A. F.; Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma; American Journal of Respiratory & Critical Care Medicine; 2005; vol. 171 (no. 6); 587-90

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Argentina
Study setting	No additional information
Study dat–s	March 2001 - September 2003
Sources of funding	Supported by GlaxoSmithKline and Trudell Medical
Inclusion criteria	Aged 6-20 months Asthmatic symptoms, defined as ≥3 episodes of wheeze with clinical improvement after receiving bronchodilators, family history of asthma or any other clinical findings indicating atopy in one or both parents and decreased pulmonary function
Exclusion criteria	Any other chronic respiratory illness
Recruitment / selection of participants	No additional information
Intervention(s)	Participants allocated to the intervention arm received 125 mcg fluticasone propionate, administered as one inhalation twice per day (morning and evening)

Population subgroups	**Treatment status** Not reported **Asthma history** Not reported
Comparator	Participants allocated to the comparator arm received a placebo inhaler, administered as one inhalation twice per day (morning and evening)
Number of participants	31 randomised 16 allocated to ICS+SABA, 14 completed 15 allocated to SABA prn, 12 completed
Duration of follow-up	6 months
Indirectness	None
Additional comments	Complete case analysis

Study arms

SABA prn plus regular ICS (N = 14)
125 mcg fluticasone propionate, one inhalation twice per day

SABA prn (N = 12)
Placebo inhaler taken as one inhalation twice per day

Characteristics

Arm-level characteristics

Characteristic	SABA prn plus regular ICS (N = 14)	SABA prn (N = 12)
% Female Sample size	n = 12 ; % = 86	n = 9 ; % = 75
Mean age (SD) (Months) Mean (SD)	12.9 (4)	14 (4)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints
- Baseline
- 6 month

Continuous Outcomes

Outcome	SABA prn plus regular ICS, Baseline, N = 14	SABA prn plus regular ICS, 6 month, N = 14	SABA prn, Baseline, N = 12	SABA prn, 6 month, N = 12
Reliever/rescue medication use (days with SABA use) (%) Final values Mean (SD)	NR (NR)	8.6 (6)	NR (NR)	16.3 (9)

Reliever/rescue medication use (days w–th SABA us–) - Polarity - Lower values are better

Criti–al appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Contin–ous Outcomes - Reliever/rescue medication use (days with SABA use)— Mean (SD) - SABA prn plus regular ICS-SABA prn-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to regular treatment not monitored and 16% missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

SABA vs ICS+SABA (young people and adults ≥12 years)

Figure 2: Severe exacerbations at > 3 months (final values, lower is better)

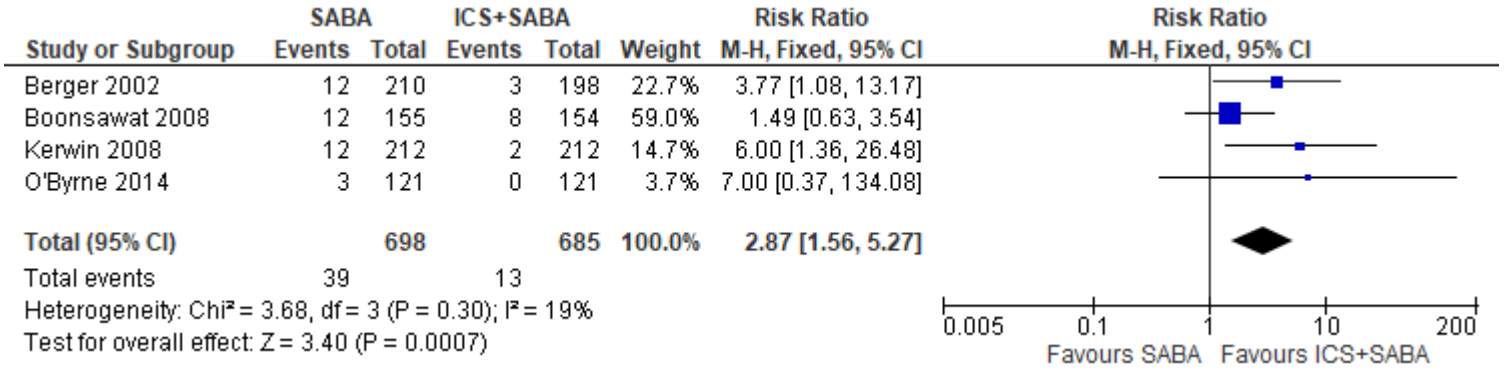


Figure 3: Severe exacerbations at > 6 months (final values, lower is better)

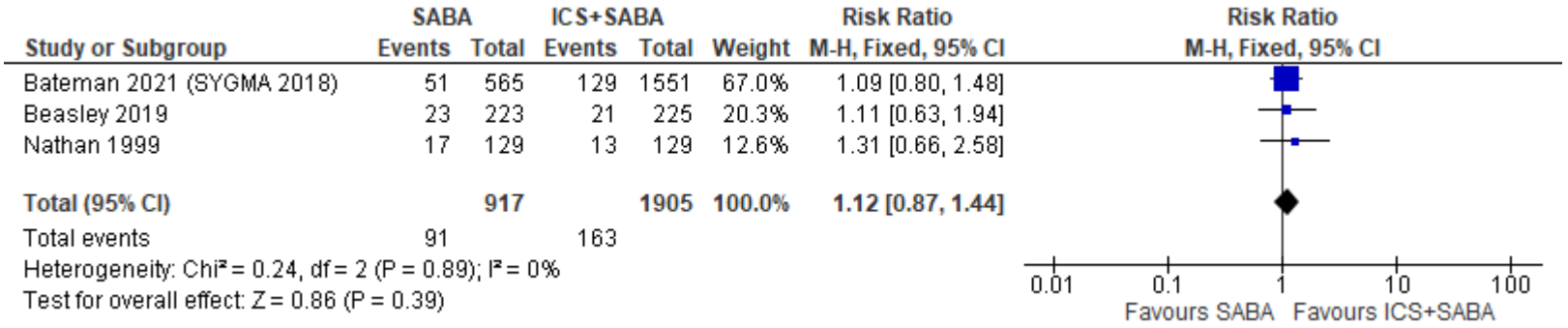


Figure 4: Mortality (adverse events resulting in death, final values, lower is better)

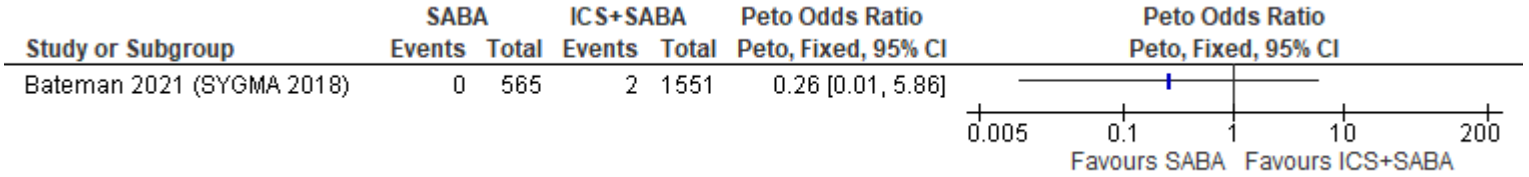


Figure 5: Quality of life (Asthma quality of life questionnaire, scale range 1-7, change scores, higher is better)

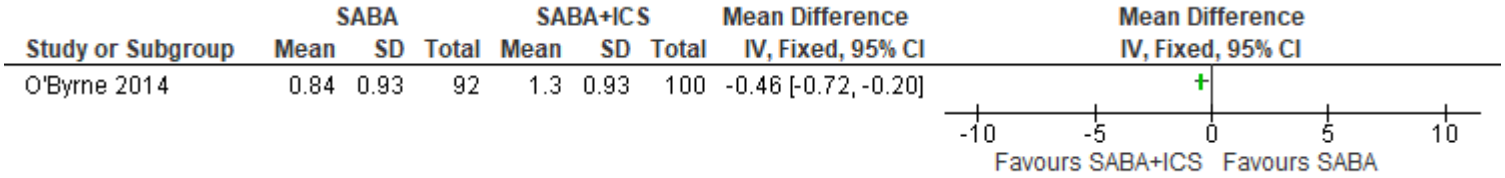


Figure 6: Asthma control (Asthma control questionnaire, scale range 0-6, mixed values, lower is better)

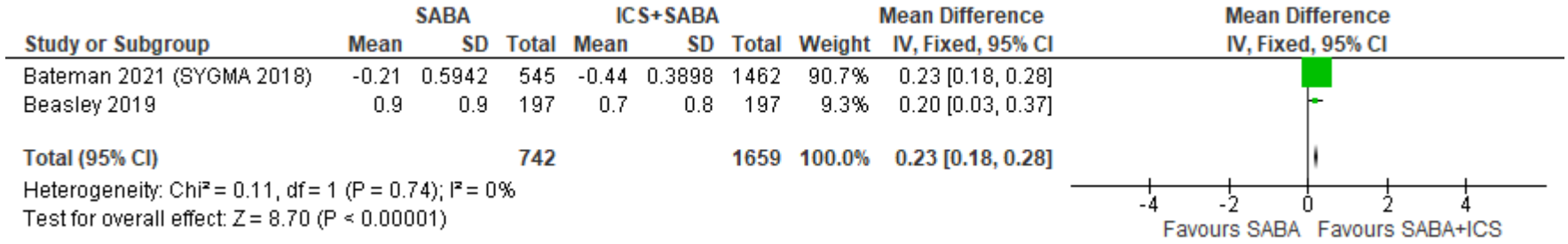


Figure 7: Asthma control (Asthma control test, scale range 5-25, change scores, lower is better)

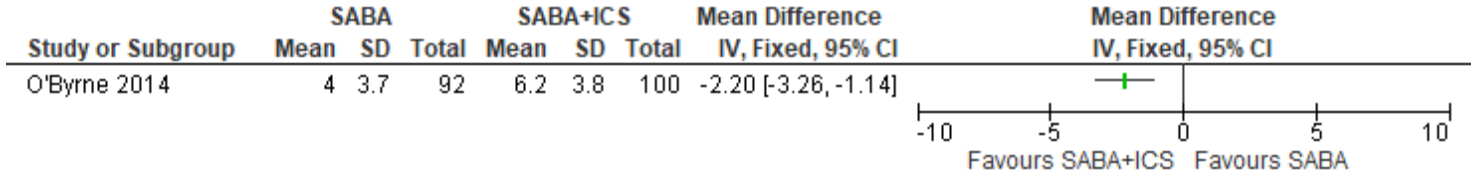


Figure 8: Reliever/rescue medication use (SABA use, puffs per day, mixed values, lower is better)

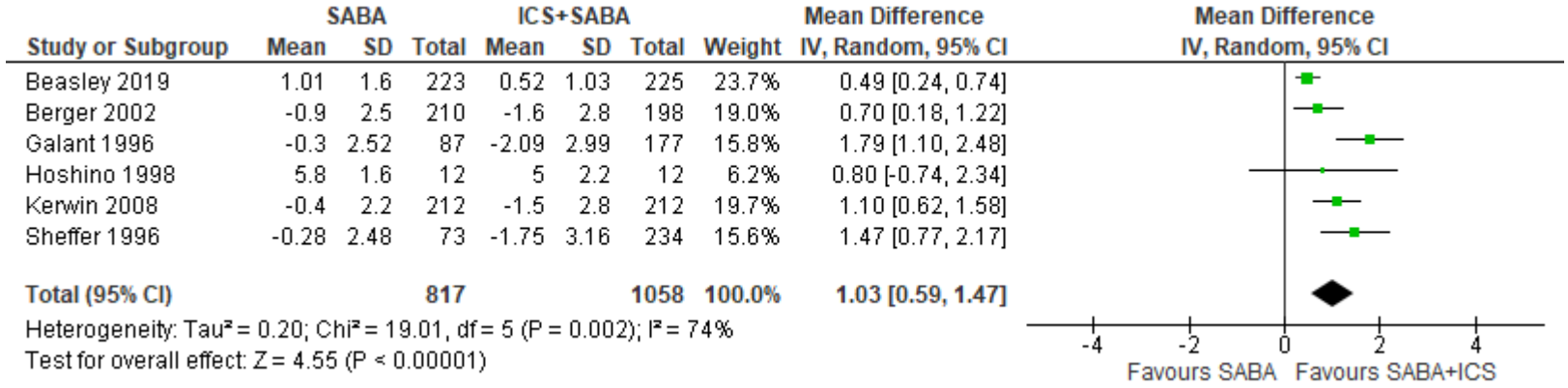


Figure 9: Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)

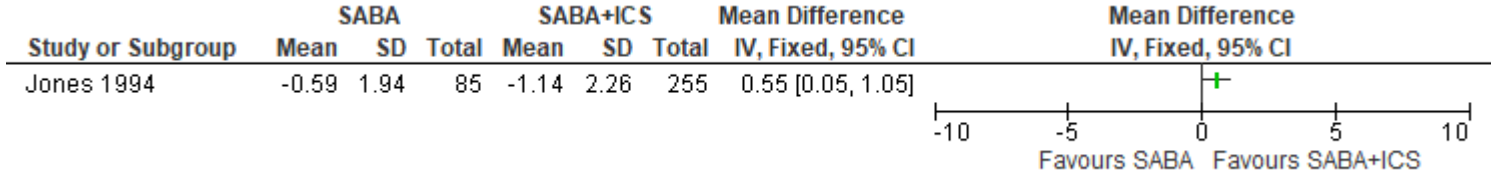


Figure 10: Reliever/rescue medication use (nighttime SABA use, puffs per day, change scores, lower is better)

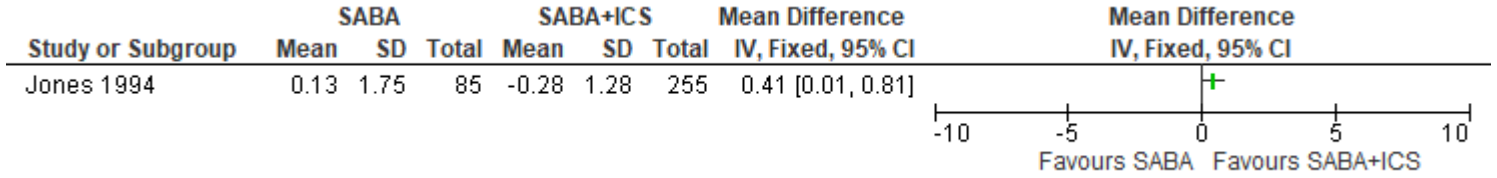


Figure 11:Reliever/rescue medication use (% SABA-free nights, change scores, higher is better)

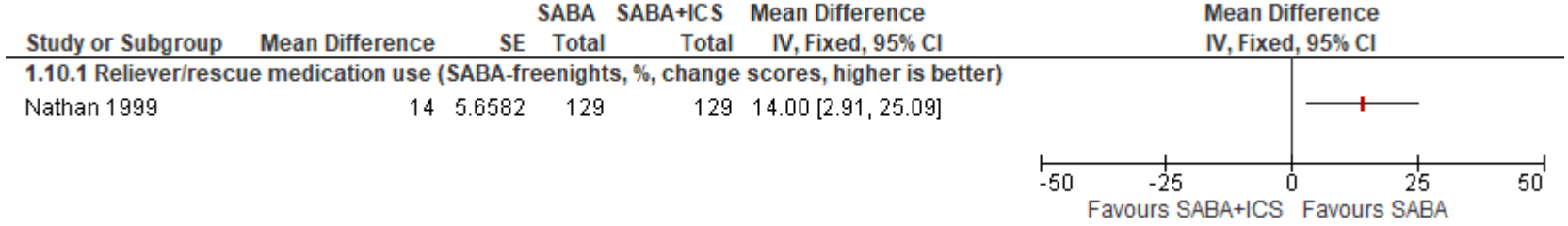


Figure 12:Reliever/rescue medication use (% SABA-free days, change scores, higher is better)

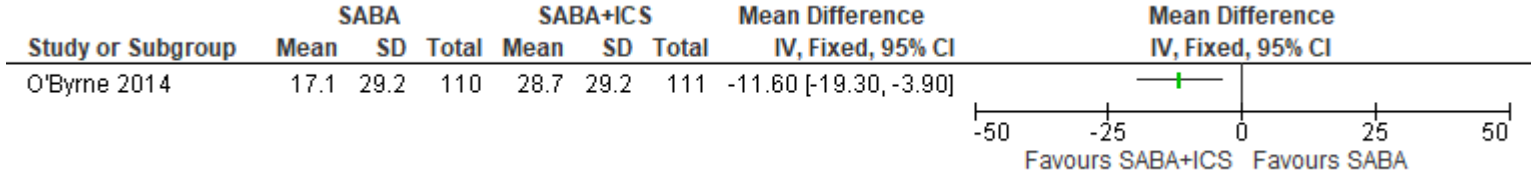


Figure 13: Lung function (FEV1 % predicted, mixed values, higher is better)

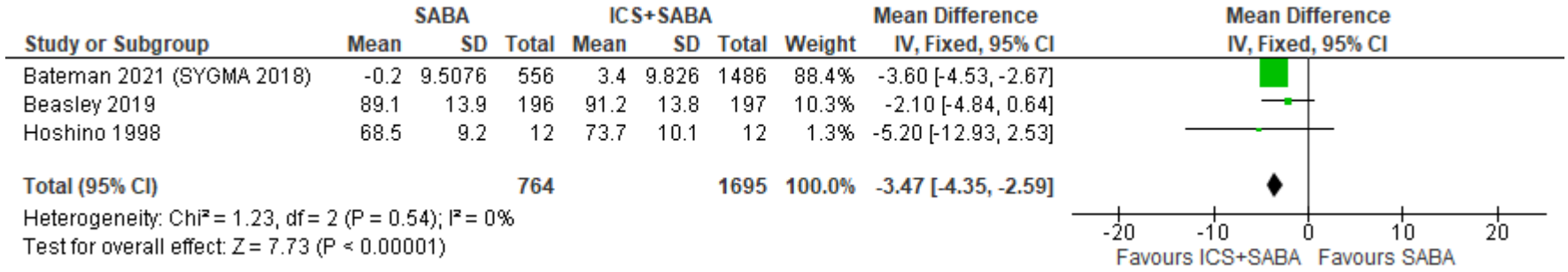


Figure 14:Lung function (FEV1, Litres, change scores, higher is better)

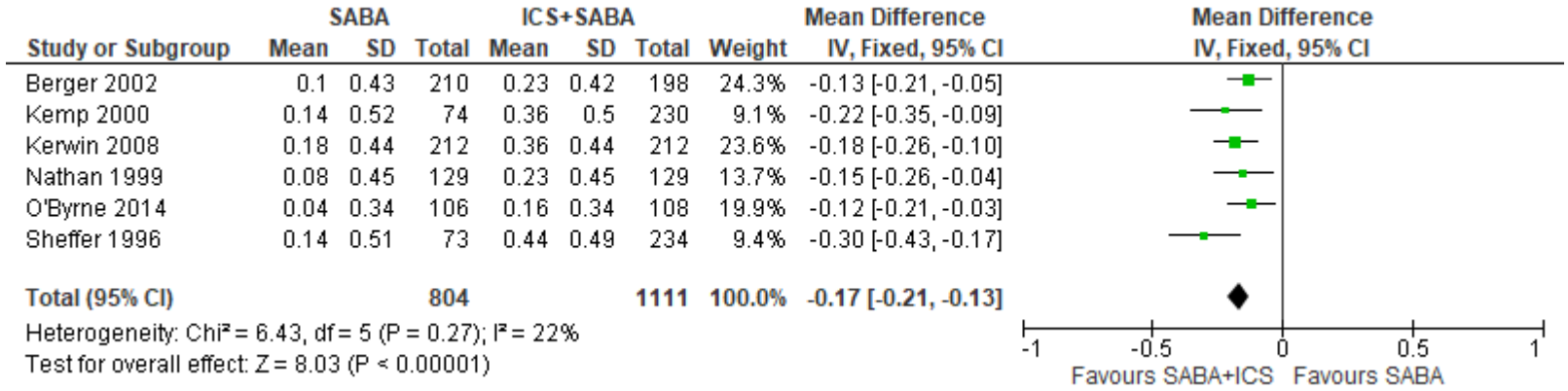


Figure 15:Lung function (PEF, L/min, mixed values, higher is better)

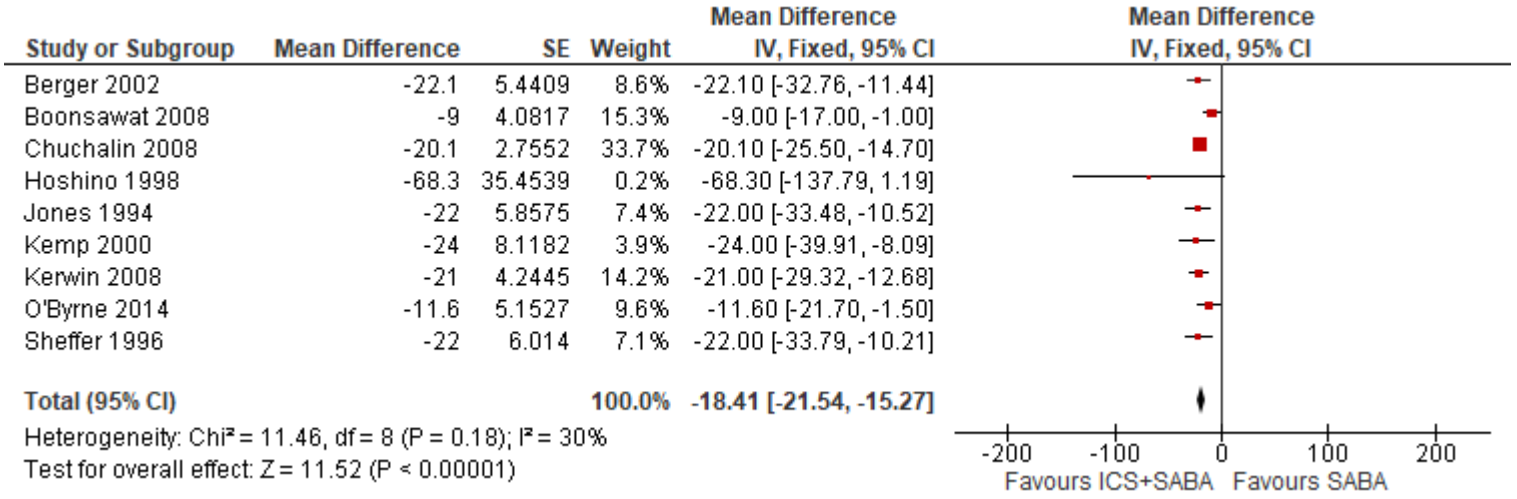


Figure 16: Adverse events (final values, lower is better)

Study or Subgroup	SABA Events	SABA Total	ICS+SABA Events	ICS+SABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bateman 2021 (SYGMA 2018)	236	565	665	1551	38.5%	0.97 [0.87, 1.09]
Boonsawat 2008	74	155	57	154	6.2%	1.29 [0.99, 1.68]
Chuchalin 2008	190	315	568	970	30.2%	1.03 [0.93, 1.14]
Galant 1996	10	87	35	177	2.5%	0.58 [0.30, 1.12]
Jones 1994	17	85	70	255	3.8%	0.73 [0.46, 1.17]
Kemp 2000	14	74	53	232	2.8%	0.83 [0.49, 1.40]
Kerwin 2008	110	212	112	212	12.1%	0.98 [0.82, 1.18]
O'Byrne 2014	46	121	37	121	4.0%	1.24 [0.87, 1.77]
Total (95% CI)		**1614**		**3672**	**100.0%**	**1.00 [0.93, 1.07]**
Total events	697		1597			

Heterogeneity: Chi² = 10.50, df = 7 (P = 0.16); I² = 33%

Test for overall effect: Z = 0.02 (P = 0.98)

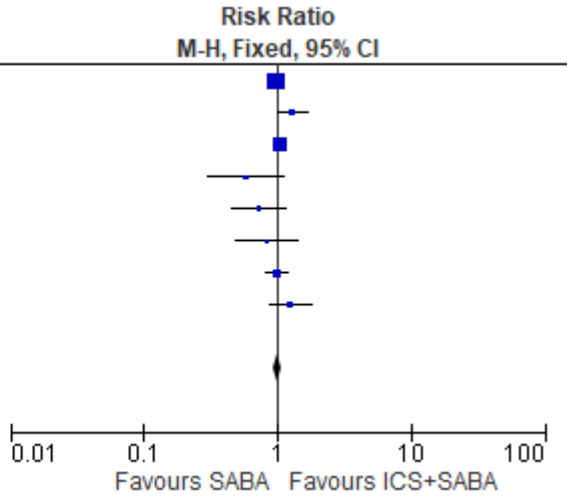


Figure 17:Pneumonia (including RTIs, final values, lower is better)

Study or Subgroup	SABA Events	SABA Total	ICS+SABA Events	ICS+SABA Total	Weight	Risk Difference M-H, Random, 95% CI
Chuchalin 2008	15	315	40	970	40.7%	0.01 [-0.02, 0.03]
Jones 1994	17	85	28	255	13.4%	0.09 [-0.00, 0.18]
O'Byrne 2014	0	121	0	121	46.0%	0.00 [-0.02, 0.02]
Total (95% CI)		**521**		**1346**	**100.0%**	**0.01 [-0.03, 0.05]**
Total events	32		68			

Heterogeneity: Tau² = 0.00; Chi² = 9.21, df = 2 (P = 0.01); I² = 78%

Test for overall effect: Z = 0.72 (P = 0.47)

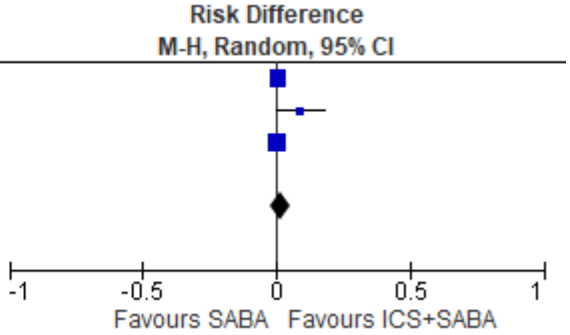
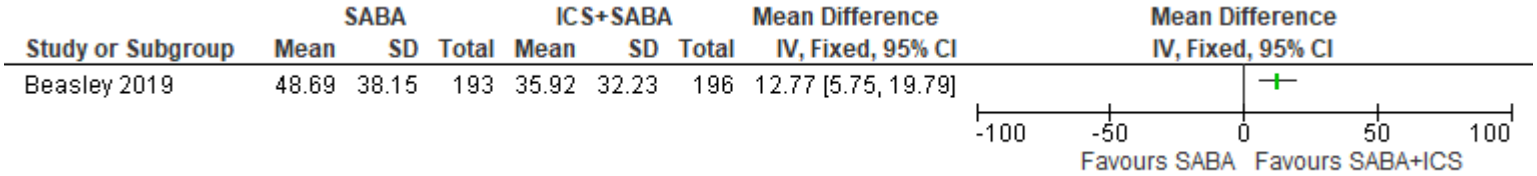


Figure 18: Inflammatory markers (FeNO, final values, lower is better)



E.2 SABA vs ICS Combination Inhaler as needed (young people and adults ≥12 years)

Figure 19: Severe asthma exacerbations (requiring course of systemic glucocorticoids, final values, lower is better)

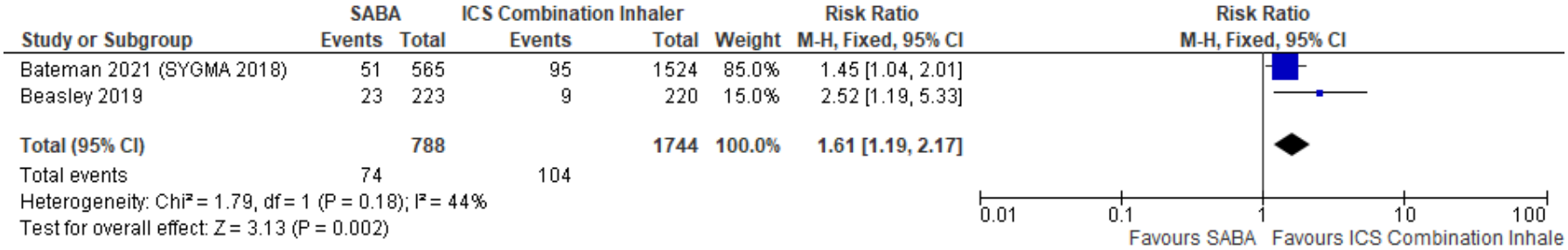


Figure 20: Mortality (adverse events resulting in death, final values, lower is better)

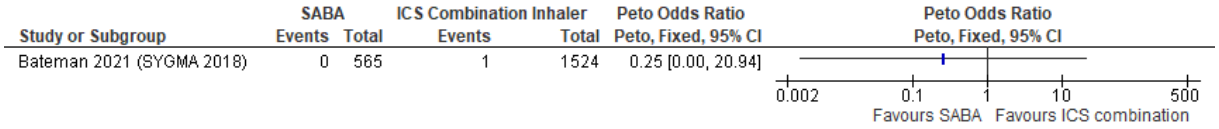


Figure 21: Asthma control (Asthma Control Questionnaire-5, scale range: 0-6, mixed values, lower is better)t

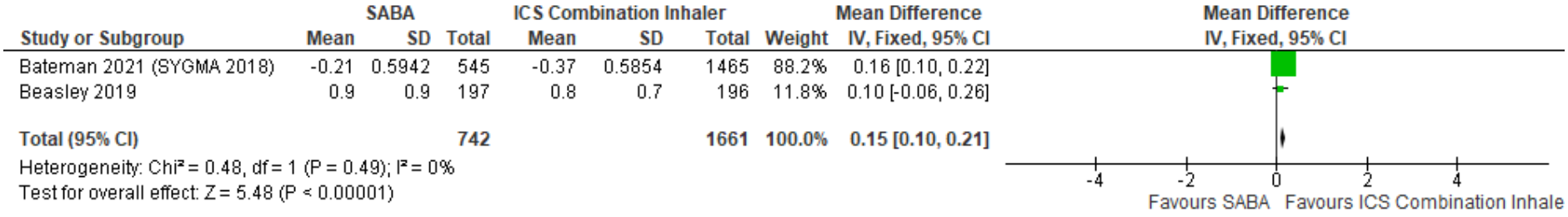


Figure 22: Reliever medication use (number of beta-2-agonist-containing actuations per day, final values, lower is better)

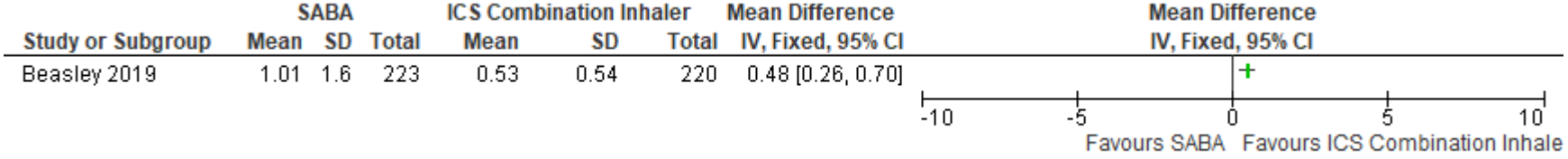


Figure 23: Lung function (% predicted FEV1, mixed values, higher is better)

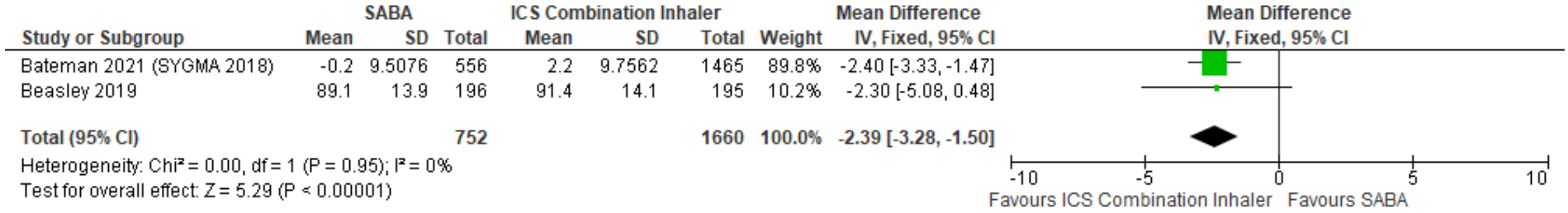


Figure 24: Adverse events (final values, lower is better)

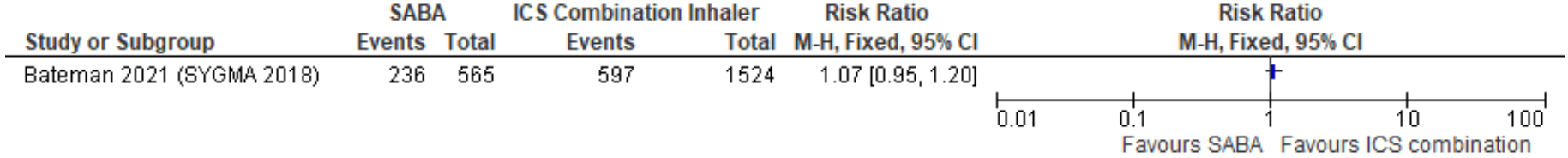
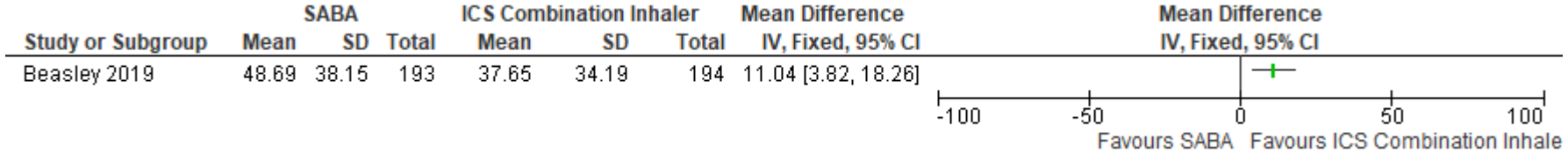


Figure 25: Inflammatory markers (FeNO, final values, lower is better)



E.3 ICS+SABA vs ICS Combination Inhaler as needed (young people and adults ≥12 years)

Figure 26: Severe asthma exacerbations (requiring course of systemic glucocorticoids, final values, lower is better)

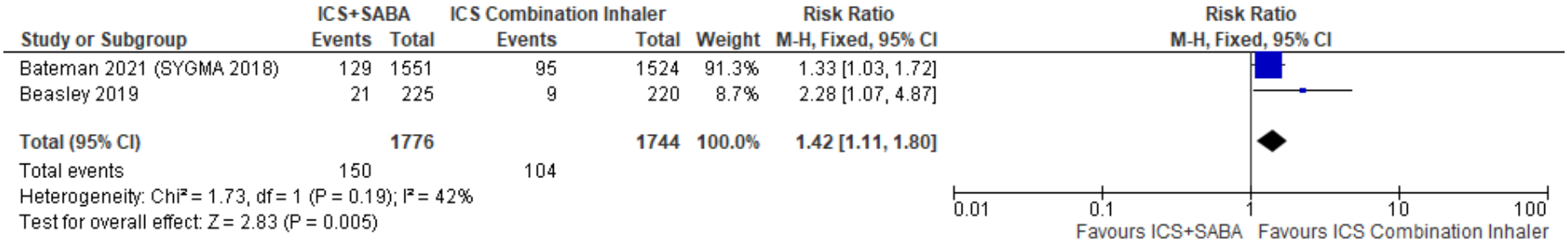


Figure 27: Mortality (adverse events resulting in death, final values, lower is better)

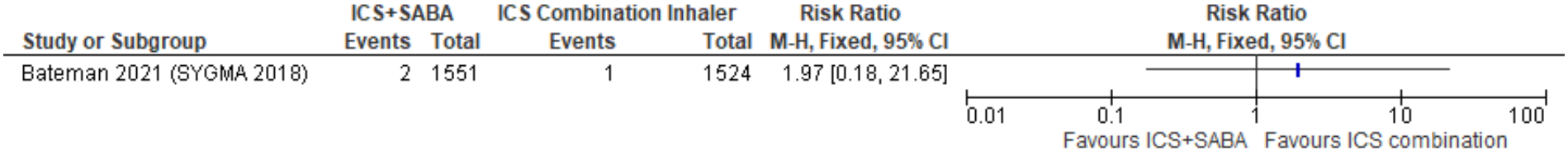


Figure 28: Asthma control (Asthma Control Questionnaire-5, scale range: 0-6, mixed values, lower is better)

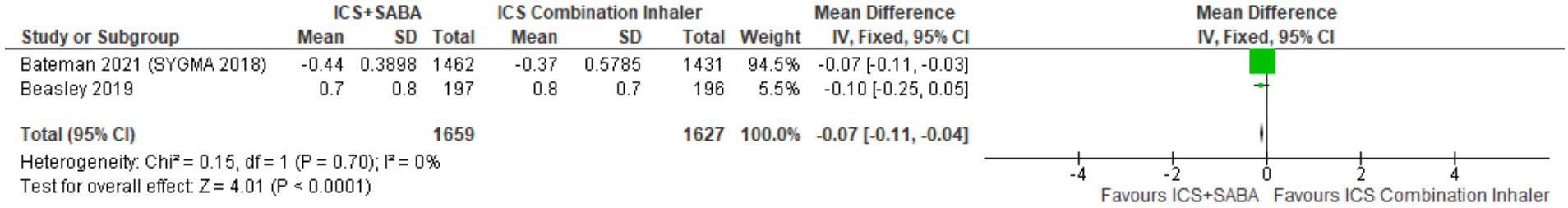


Figure 29: Reliever medication use (number of beta-2-agonist-containing actuations per day, final values, lower is better)

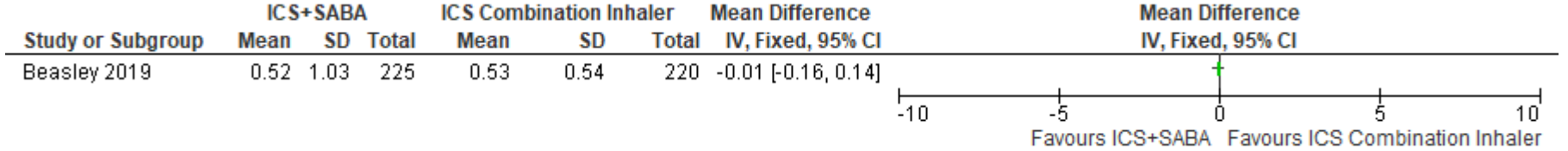


Figure 30: Lung function (% predicted FEV1, mixed values, higher is better)

Study or Subgroup	ICS+SABA Mean	SD	Total	ICS Combination Inhaler Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bateman 2021 (SYGMA 2018)	3.4	9.826	1486	2.2	9.7562	1465	93.9%	1.20 [0.49, 1.91]
Beasley 2019	91.2	13.8	197	91.4	14.1	195	6.1%	-0.20 [-2.96, 2.56]
Total (95% CI)			**1683**			**1660**	**100.0%**	**1.11 [0.43, 1.80]**

Heterogeneity: Chi² = 0.93, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 3.19 (P = 0.001)

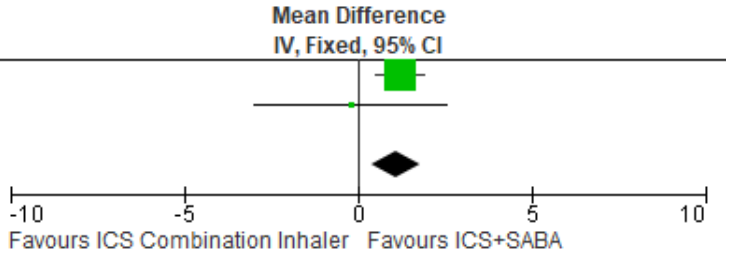


Figure 31: Adverse events (final values, lower is better)

Study or Subgroup	ICS+SABA Events	Total	ICS Combination Inhaler Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bateman 2021 (SYGMA 2018)	665	1551	597	1524	1.09 [1.01, 1.19]

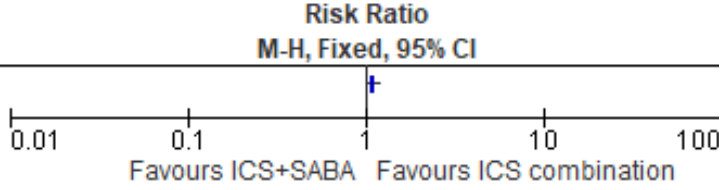
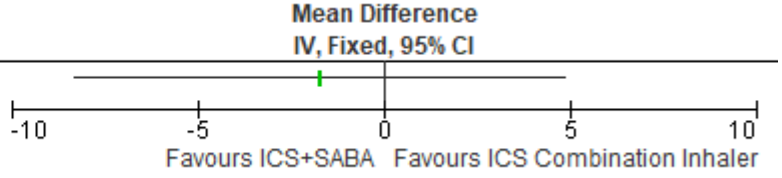


Figure 32: Inflammatory markers (FeNO, final values, lower is better)

Study or Subgroup	ICS+SABA Mean	SD	Total	ICS Combination Inhaler Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Beasley 2019	35.92	32.23	196	37.65	34.19	194	-1.73 [-8.33, 4.87]



E.4 SABA vs ICS+SABA in children 5-11 years

Figure 33: Severe exacerbations at > 3 months (final values, lower is better)

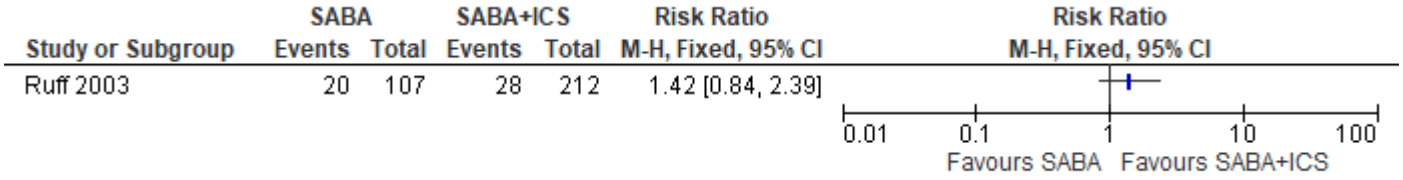


Figure 34:Adverse events (final values, lower is better)

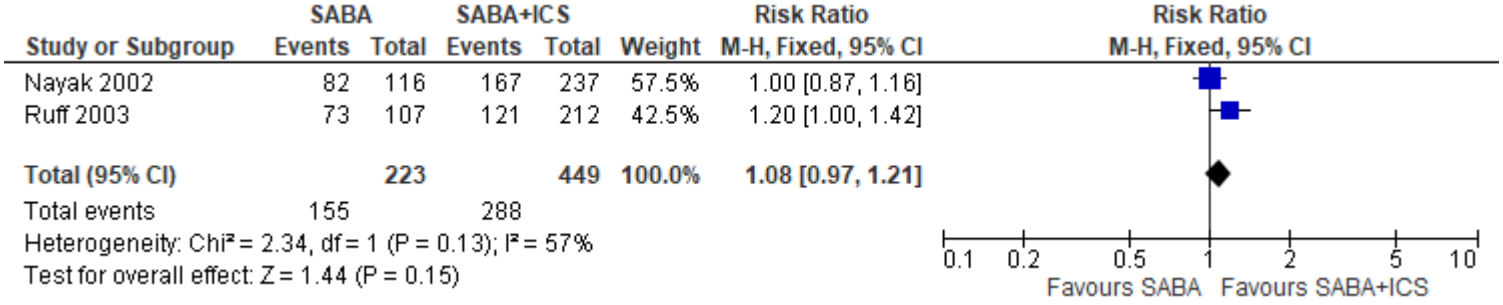


Figure 35:Adrenal insufficiency (abnormal response to low-dose ACTH stimulation, final values, lower is better)

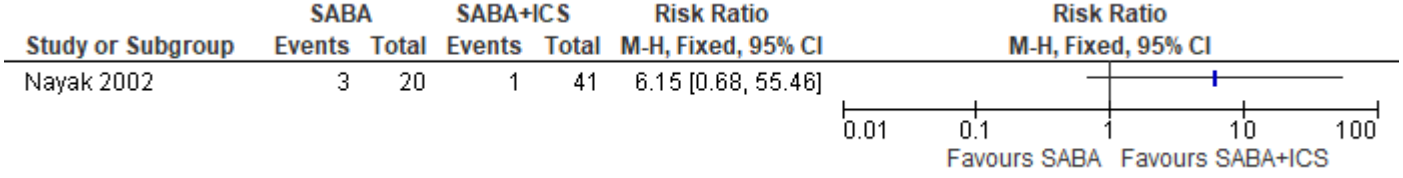
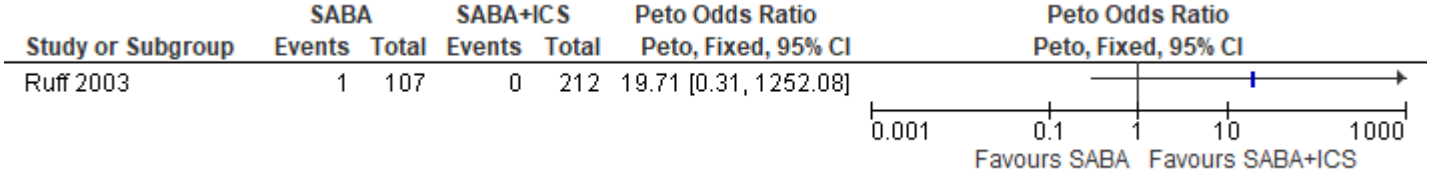


Figure 36:Pneumonia (final values, lower is better)



E.5 SABA vs ICS+SABA in children <5 years

Figure 37: Hospital admissions at >6 months (final values, lower is better)

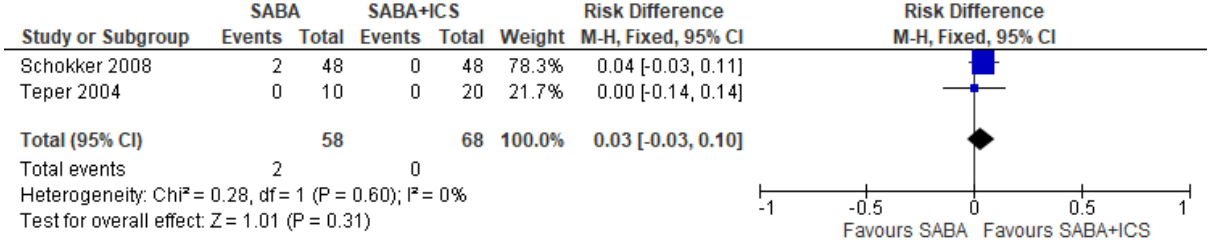


Figure 38: Reliever/rescue medication use (SABA use, puffs per day, change scores, lower is better)

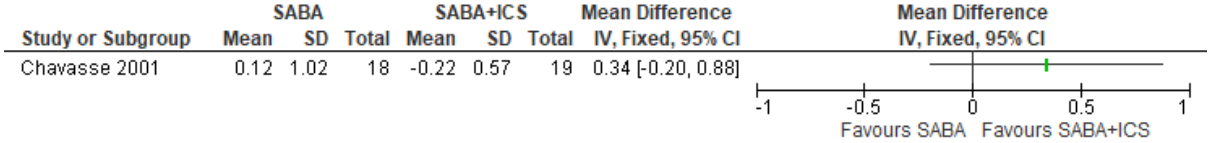


Figure 39: Reliever/rescue medication use (daytime SABA use, puffs per day, mixed values, lower is better)

Study or Subgroup	SABA Mean	SABA SD	SABA Total	SABA+ICS Mean	SABA+ICS SD	SABA+ICS Total	Weight	Mean Difference IV, Random, 95% CI
Papi 2009	-0.09	0.42	53	-0.24	0.44	108	62.8%	0.15 [0.01, 0.29]
Schokker 2008	0.31	0.5	46	0.37	0.71	46	37.2%	-0.06 [-0.31, 0.19]
Total (95% CI)			**99**			**154**	**100.0%**	**0.07 [-0.13, 0.27]**

Heterogeneity: Tau² = 0.01; Chi² = 2.05, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 0.71 (P = 0.48)

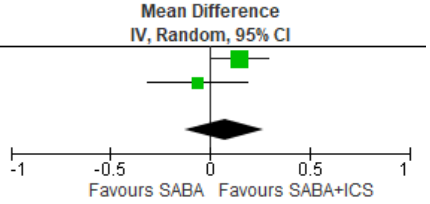


Figure 40: Reliever/rescue medication use (nighttime SABA use, puffs per night, mixed values, lower is better)

Study or Subgroup	SABA Mean	SABA SD	SABA Total	SABA+ICS Mean	SABA+ICS SD	SABA+ICS Total	Weight	Mean Difference IV, Fixed, 95% CI
Papi 2009	-0.08	0.25	53	-0.1	0.21	108	60.0%	0.02 [-0.06, 0.10]
Schokker 2008	0.06	0.14	46	0.11	0.3	46	40.0%	-0.05 [-0.15, 0.05]
Total (95% CI)			**99**			**154**	**100.0%**	**-0.01 [-0.07, 0.05]**

Heterogeneity: Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 0.26 (P = 0.80)

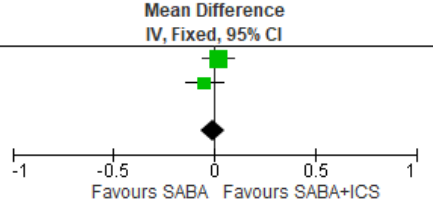


Figure 41: Reliever/rescue medication use (days with SABA use, final values, lower is better)

Study or Subgroup	SABA Mean	SABA SD	SABA Total	SABA+ICS Mean	SABA+ICS SD	SABA+ICS Total	Weight	Mean Difference IV, Random, 95% CI
Teper 2004	24.3	1.3	10	7.8	1.5	20	55.8%	16.50 [15.46, 17.54]
Teper 2005	16.3	9	12	8.6	6	14	44.2%	7.70 [1.72, 13.68]
Total (95% CI)			**22**			**34**	**100.0%**	**12.61 [4.05, 21.18]**

Heterogeneity: Tau² = 33.92; Chi² = 8.06, df = 1 (P = 0.005); I² = 88%
Test for overall effect: Z = 2.89 (P = 0.004)

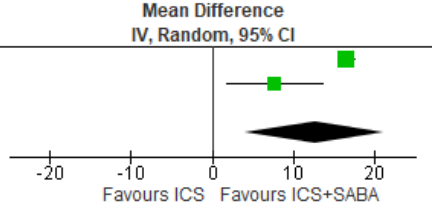
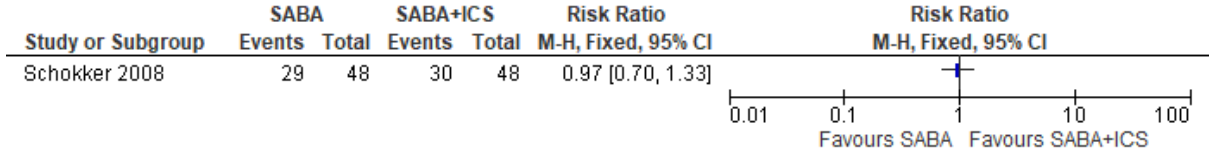


Figure 42: Adverse events (final values, lower is better)



E.6 SABA vs ICS combination inhalers in children <5 years

Figure 43: Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)

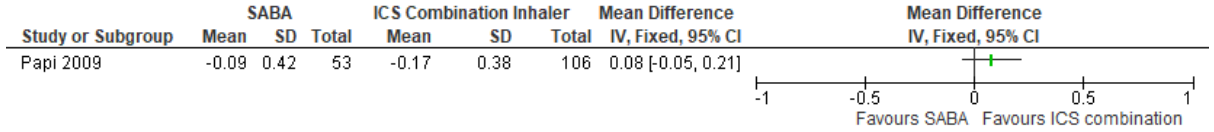
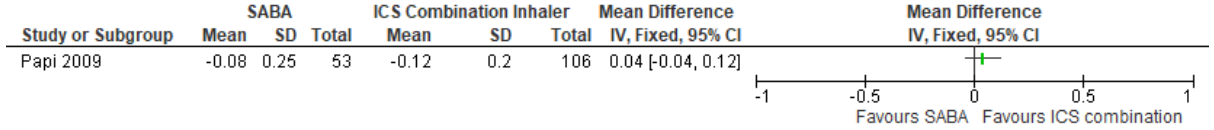


Figure 44: Reliever/rescue medication use (nighttime SABA use, puffs per night, change scores, lower is better)



E.7 ICS+SABA vs ICS combination inhalers as needed in children <5 years

Figure 45: Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)

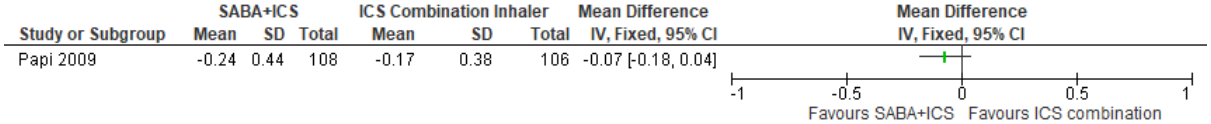
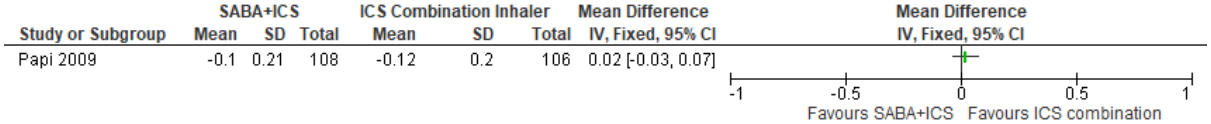


Figure 46: Reliever/rescue medication use (nighttime SABA use, puffs per night, change scores, lower is better)



Appendix F – GRADE tables

Table 18: Clinical evidence profile: SABA vs ICS+SABA (young people and adults, ≥12 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in adults	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at >3 months (final values, lower is better)												
4	randomised trials	serious[a]	not serious	not serious	not serious	none	39/698 (5.6%)	13/685 (1.9%)	**RR 2.87** (1.56 to 5.27)	**35 more per 1,000** (from 11 more to 81 more)	⨁⨁⨁◯ Moderate	CRITICAL
Severe asthma exacerbations at >6 months (final values, lower is better)												
3	randomised trials	very serious[b]	not serious	not serious	serious[c]	none	91/917 (9.9%)	163/1905 (8.6%)	**RR 1.12** (0.87 to 1.44)	**10 more per 1,000** (from 11 fewer to 38 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (adverse events resulting in death, final values, lower is better)												
1	randomised trials	very serious[b]	not serious	not serious	very serious[d]	none	0/565 (0.0%)	2/1551 (0.1%)	**OR 0.26** (0.01 to 5.86)	**0 fewer per 1,000** (from 0 fewer to 0 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Asthma quality of life questionnaire, scale range: 1-7, change scores, higher is better)												
1	randomised trials	very serious[e]	not serious	serious[f]	serious[g]	none	92	100	-	MD **0.46 lower** (0.72 lower to 0.2 lower)	⨁◯◯◯ Very low	CRITICAL
Asthma control (Asthma Control Questionnaire-5, scale range 0-6, mixed values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in adults	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious[b]	not serious	not serious	not serious	none	742	1659	-	MD **0.23 higher** (0.18 higher to 0.28 higher)	⨁⨁◯◯ Low	CRITICAL
Asthma control (Asthma control test, scale range: 5-25, change scores, higher is better)												
1	randomised trials	very serious[e]	not serious	serious[f]	serious[h]	none	92	100	-	MD **2.2 lower** (3.26 lower to 1.14 lower)	⨁◯◯◯ Very low	CRITICAL
Reliever medication use (SABA use, puffs per day, mixed values, lower is better)												
6	randomised trials	very serious[i]	serious[j]	not serious	serious[k]	none	817	1058	-	MD **1.03 higher** (0.59 higher to 1.47 higher)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)												
1	randomised trials	very serious[l]	not serious	not serious	not serious	none	85	255	-	MD **0.55 higher** (0.05 higher to 1.05 higher)	⨁⨁◯◯ Low	CRITICAL
Reliever/rescue medication use (night time SABA use, puffs per night, change scores, lower is better)												
1	randomised trials	very serious[l]	not serious	not serious	serious[m]	none	85	255	-	MD **0.41 higher** (0.01 higher to 0.81 higher)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (% SABA-free nights, change scores, higher is better)												
1	randomised trials	very serious[n]	not serious	serious[o]	serious[p]	none	129	129	-	MD **14 higher** (2.91 higher to 25.09 higher)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (% SABA-free days, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in adults	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[e]	not serious	not serious	serious[q]	none	110	111	-	MD **11.6 lower** (19.3 lower to 3.9 lower)	⨁⨁◯◯ Low	CRITICAL
Lung function (% predicted FEV1, mixed values, higher is better)												
3	randomised trials	serious[b]	not serious	not serious	not serious	none	764	1695	-	MD **3.47 lower** (4.35 lower to 2.59 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (FEV1, litres, change scores, higher is better)												
6	randomised trials	very serious[r]	not serious	not serious	not serious	none	804	1111	-	MD **0.17 L lower** (0.21 lower to 0.13 lower)	⨁⨁◯◯ Low	CRITICAL
Lung function (PEF, L/min, mixed values, higher is better)												
9	randomised trials	very serious[i]	not serious	not serious	serious[s]	none	210	198	-	MD **18.41 change score lower** (21.54 lower to 15.27 lower)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												
8	randomised trials	serious[a]	not serious	not serious	not serious	none	697/1614 (43.2%)	1597/3672 (43.5%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 30 fewer to 30 more)	⨁⨁⨁◯ Moderate	CRITICAL
Pneumonia (incl RTI, final values, lower is better)												
3	randomised trials	not serious	serious[i]	not serious	very serious[t]	none	32/521 (6.1%)	68/1346 (5.1%)	**RD 0.01** (-0.03 to 0.05)	10 more per 1,000 (30 fewer to 50 more)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in adults	Relative (95% CI)	Absolute (95% CI)		
Inflammatory markers (FeNO, final values, lower is better)												
1	randomised trials	serious[u]	not serious	not serious	not serious	none	193	196	-	MD **12.77 ppb higher** (5.75 higher to 19.79 higher)	⨁⨁⨁◯ Moderate	CRITICAL

a. Downgraded by one increment because there are some concerns about risk of bias for the majority of studies (randomisation method and adherence to maintenance treatment not monitored)

b. Downgraded by two increments because the majority of evidence at high risk of bias [unclear method of randomisation and allocation concealment; no information on handling of switching groups, including how handled in analysis (switching likely due to clinician being able to add ICS to SABA treatment arm if exacerbations occurred)]

c. Downgraded by one increment for imprecision because the 95%CI crosses one MID (0.8 to 1.25)

d. Downgraded by two increments for imprecision because the 95%CI crosses both MIDs (0.8 to 1.25)

e. Downgraded by two increments because the study was at high risk of bias (14% missing outcome data, 7% difference between dropout rates per study arm and reasons for discontinuation that could have been related to participant's health status)

f. Downgraded by one increment for population indirectness (participants could have been treated with SABA, LTRAs or a combination prior to screening)

g. Downgraded by one increment for imprecision because the 95%CI crosses one MID (published MID=0.5)

h. Downgraded by one increment for imprecision because the 95%CI crosses one MID (published MID=3)

i. Downgraded by two increments because the majority of evidence is at high risk of bias (randomisation method not reported, adherence to regular treatment not monitored, high dropout rates, considerable difference in dropout rates between arms and reasons for discontinuation related to participant's health status)

j. Downgraded by one increment because of unexplained heterogeneity (I squared>70%)

k. Downgraded by one increment for imprecision because the 95%CI crosses one MID (published MID=0.81)

l. Downgraded by two increments because the study is at high risk of bias (22% missing outcome data with no information on dropout rates per study arm and reasons for discontinuation potentially related to participant's health status).

m. Downgraded by one increment for imprecision because the 95%CI crosses one MID (calculated as final SD/2=0.78)

n. Downgraded by two increments because the study is at high risk of bias (randomisation method not reported, adherence to maintenance therapy not reported, 20% dropout rate with reasons for discontinuation potentially related to participant's health status)

o. Downgrade by one increment for population indirectness (participants could have been receiving intranasal corticosteroids or intranasal cromolyn sodium at screening and were allowed to maintain this treatment at a constant dose)

p. Downgraded by one increment for imprecision because 95%CI crosses MID (calculated as final SD of both arms/2=22.72)

q. Downgraded by one increment for imprecision because the 95%CI crosses one MID (calculated as final SD of both arms/2=14.6)

r. Downgraded by two increments because the majority of evidence is at high risk of bias (randomisation method and adherence to maintenance therapy not reported, missing data and high dropout rate with reasons for discontinuation related to participant's health status)

s. Downgraded by one increment for imprecision because the confidence interval crosses one MID (published MID=18.79)

t. Downgraded by one increment for imprecision due to zero events and small sample size.

u. Downgraded by one increment because of some concerns about risk of bias due to missing outcome data.

Table 19: Clinical evidence profile: SABA vs ICS Combination Inhaler as needed (young people and adults, ≥12 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS Combination Inhaler	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations (final values, lower is better)												
2	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	74/788 (9.4%)	104/1744 (6.0%)	**RR 1.61** (1.19 to 2.17)	**36 more per 1,000** (from 11 more to 70 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (adverse events resulting in death, final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	0/565 (0.0%)	1/1524 (0.1%)	**RR 0.25** (0.0 to 20.94)	**1 fewer per 1,000** (from 1 fewer to 14 more)	⨁◯◯◯ Very low	CRITICAL
Asthma control (Asthma Control Questionnaire-5, scale 0-6, mixed values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS Combination Inhaler	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious[a]	not serious	not serious	not serious	none	742	1661	-	MD **0.15 higher** (0.1 higher to 0.21 higher)	⨁⨁◯◯ Low	CRITICAL
Reliever medication use (number of beta-2-agonist-containing actuations per day, final values, lower is better)												
1	randomised trials	not serious	not serious	not serious	not serious	none	223	220	-	MD **0.48 higher** (0.26 higher to 0.7 higher)	⨁⨁⨁⨁ High	CRITICAL
Lung function (% predicted FEV1, mixed values, higher is better)												
2	randomised trials	very serious[a]	not serious	not serious	not serious	none	752	1660	-	MD **2.39 lower** (3.28 lower to 1.5 lower)	⨁⨁◯◯ Low	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	236/565 (41.8%)	597/1524 (39.2%)	**RR 1.07** (0.95 to 1.20)	**27 more per 1,000** (from 20 fewer to 78 more)	⨁⨁◯◯ Low	CRITICAL
Inflammatory markers (FeNO, final values, lower is better)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	193	194	-	MD **11.04 higher** (3.82 higher to 18.26 higher)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS Combination Inhaler	Relative (95% CI)	Absolute (95% CI)		

a. Downgraded by 2 increments due to bias arising from the randomisation process and deviations from the intended interventions

b. Downgraded by 1 increment if the confidence intervals crossed one MID and 2 increments if the confidence intervals crossed both MIDs

c. Downgraded by 1 increment due to bias arising from missing outcome data

Table 20: Clinical evidence profile: ICS+SABA vs ICS Combination Inhaler as needed (young people and adults, ≥12 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS+SABA	ICS Combination Inhaler	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations (final values, lower is better)												
2	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	150/1776 (8.4%)	104/1744 (6.0%)	**RR 1.42** (1.11 to 1.80)	**25 more per 1,000** (from 7 more to 48 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (adverse events resulting in death, final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	2/1551 (0.1%)	1/1524 (0.1%)	**RR 1.97** (0.18 to 21.65)	**1 more per 1,000** (from 1 fewer to 14 more)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS+SABA	ICS Combination Inhaler	Relative (95% CI)	Absolute (95% CI)		
Asthma control (Asthma Control Questionnaire-5, scale range 0-6, mixed values, lower is better)												
2	randomised trials	very serious[aa]	not serious	not serious	not serious	none	1659	1627	-	MD **0.07 lower** (0.11 lower to 0.04 lower)	⨁⨁◯◯ Low	CRITICAL
Reliever medication use (number of beta-2-agonist-containing actuations per day, final values, lower is better)												
1	randomised trials	not serious	not serious	not serious	not serious	none	225	220	-	MD **0.01 lower** (0.16 lower to 0.14 higher)	⨁⨁⨁⨁ High	CRITICAL
Lung function (% predicted FEV1, mixed values, higher is better)												
2	randomised trials	very serious[a]	not serious	not serious	not serious	none	1683	1660	-	MD **1.11 higher** (0.43 higher to 1.8 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	665/1551 (42.9%)	597/1524 (39.2%)	**RR 1.09** (1.01 to 1.19)	**35 more per 1,000** (from 4 more to 74 more)	⨁⨁◯◯ Low	CRITICAL
Inflammatory markers (FeNO, final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS+SABA	ICS Combination Inhaler	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[b]	not serious	not serious	not serious	none	196	194	-	MD **1.73 lower** (8.33 lower to 4.87 higher)	⨁⨁⨁◯ Moderate	CRITICAL

a. Downgraded by 2 increments due to bias arising from the randomisation process and deviations from the intended interventions

b. Downgraded by 1 increment due to bias arising from missing outcome data

c. Downgraded by 1 increment if confidence intervals crossed one MID and 2 increments if confidence intervals crossed both MIDs

Table 21: Clinical evidence profile: SABA vs ICS+SABA in children aged 5-11 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in children	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at >3 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	20/107 (18.7%)	28/212 (13.2%)	**RR 1.42** (0.84 to 2.39)	**55 more per 1,000** (from 21 fewer to 184 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												
2	randomised trials	not serious	not serious	not serious	not serious	none	155/223 (69.5%)	288/449 (64.1%)	**RR 1.08** (0.97 to 1.21)	**51 more per 1,000** (from 19 fewer to 135 more)	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in children	Relative (95% CI)	Absolute (95% CI)		
Adrenal insufficiency (abnormal response to low-dose ACTH stimulation, final values, lower is better)												
1	randomised trials	very serious[c]	not serious	not serious	very serious[d]	none	3/20 (15.0%)	1/41 (2.4%)	**RR 6.15** (0.68 to 55.46)	**126 more per 1,000** (from 8 fewer to 1,000 more)	⨁◯◯◯ Very low	CRITICAL
Pneumonia (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[d]	none	1/107 (0.9%)	0/212 (0.0%)	**OR 19.71** (0.31 to 1252.08)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by two increments because study at high risk of bias (randomisation method not reported and 62.5% adherence to study medications)

b. Downgraded by one increment for imprecision because the 95% CI crosses one MID (0.8-1.25)

c. Downgraded by two increments because study at high risk of bias (subgroup analysis of participants who were willing to have blood tests with complete-case analysis used; included only participants with pre and post study measurements; dropout rates in the subgroup not reported)

d. Downgraded by two increments for imprecision because the 95%CI crosses both MIDs (0.8-1.25)

Table 22: Clinical evidence profile: SABA vs ICS+SABA in children under 5 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in infants	Relative (95% CI)	Absolute (95% CI)		
Hospital admissions at >6 months (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in infants	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	2/58 (3.4%)	0/68 (0.0%)	RD 0.03 (-0.03 to 0.10)	**30 more per 1,000** (from 30 fewer to 100 more)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (SABA use, puffs per day, change scores, lower is better)												
1	randomised trials	very serious[c]	not serious	not serious	serious[d]	none	18	19	-	MD **0.34 higher** (0.2 lower to 0.88 higher)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (daytime SABA use, puffs per day, mixed values, lower is better)												
2	randomised trials	serious[e]	serious[f]	not serious	serious[g]	none	99	154	-	MD **0.07 higher** (0.13 lower to 0.27 higher)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (night time SABA use, puffs per night, mixed values, lower is better) MID=0.11 (mean follow-up SD/2)												
2	randomised trials	serious[e]	not serious	not serious	not serious	none	99	154	-	MD **0.01 lower** (0.07 lower to 0.05 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (days with SABA use, final values, lower is better)												
2	randomised trials	very serious[h]	serious[i]	not serious	not serious	none	22	34	-	MD **12.61 higher** (4.05 higher to 21.18 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	not serious	not serious	serious[a]	very serious[i]	none	29/48 (60.4%)	30/48 (62.5%)	**RR 0.97** (0.70 to 1.33)	**19 fewer per 1,000** (from 188 fewer to 206 more)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS+SABA in infants	Relative (95% CI)	Absolute (95% CI)		

a. Downgraded by one increment for population indirectness (38% participants had previously been treated with ICS)

b. Downgraded by two increments due to inadequate sample size (optimal information size calculator power = 56%)

c. Downgraded by two increments because the study is at high risk of bias (adherence to regular treatment not monitored and 29% dropout rate with reasons potentially related to participant's health status)

d. Downgraded by one increment for imprecision because 95%CI crosses one MID (published MID=0.81)

e. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

f. Downgraded by one increment due to moderate heterogeneity that was not explained by a random effects model (I2=51%)

g. Downgraded by one increment due to the 95%CI overlapping one MID (calculated as mean follow-up SD/2 = 0.26)

h. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence to treatment not monitored), missing outcome data (12% missing with complete case analysis, and reasons for discontinuation related to participant's health status)

i. Downgraded by one increment due to unexplained heterogeneity (I squared=88%)

j. Downgraded by two increments for imprecision because 95%CI crosses both MIDs (0.8-1.25)

Table 23: Clinical evidence profile: SABA vs ICS combination inhaler as needed in children under 5 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS combination	Relative (95% CI)	Absolute (95% CI)		
Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	53	106	-	MD **0.08 higher** (0.05 lower to 0.21 higher)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA	ICS combination	Relative (95% CI)	Absolute (95% CI)		
Reliever/rescue medication use (night time SABA use, puffs per night, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	53	106	-	MD **0.04 higher** (0.04 lower to 0.12 higher)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

b. Downgraded by one increment due to the 95%CI overlapping one MID (calculated as mean follow-up SD/2 = 0.2)

c. Downgraded by one increment due to the 95%CI overlapping one MID (calculated as mean follow-up SD/2 = 0.11)

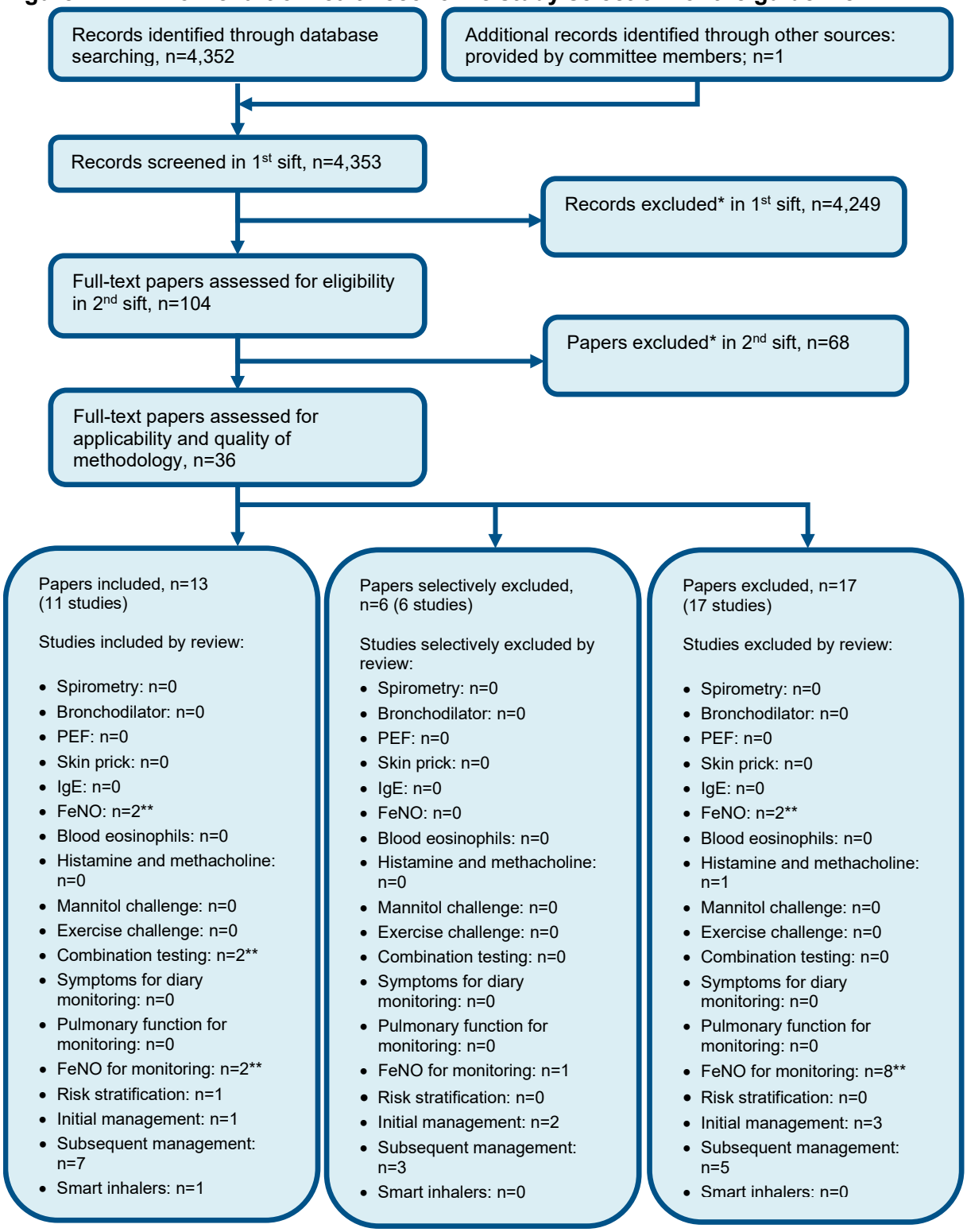
Table 24: Clinical evidence profile: ICS+SABA vs ICS combination inhaler as needed in children under 5 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABA+ICS	ICS combination	Relative (95% CI)	Absolute (95% CI)		
Reliever/rescue medication use (daytime SABA use, puffs per day, change scores, lower is better) MID= 0.21 (follow-up SD/2)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	108	106	-	MD **0.07 lower** (0.18 lower to 0.04 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (night time SABA use, puffs per night, change scores, lower is better) MID= 0.10 (follow-up SD/2)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	108	106	-	MD **0.02 higher** (0.03 lower to 0.07 higher)	⨁⨁⨁◯ Moderate	CRITICAL

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

Appendix G – Economic evidence study selection

Figure 47: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

** Includes studies that are in multiple reviews

Appendix H Economic evidence tables

Study	FitzGerald 2020(FitzGerald et al., 2020)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcomes: QALYs) **Study design:** Cost-utility analysis based on results from SYGMA 2 RCT(Bateman et al., 2018). **Approach to analysis:** A Markov model with three states representing three different types of severe exacerbations was developed using trial data. The model used weekly cycle to reflect frequency and duration of asthma exacerbations. **Perspective:** UK NHS **Time horizon:** Lifetime	**Population:** Asthma patients aged ≥ 12 years with asthma uncontrolled on as-needed SABA (46%) or controlled on regular low-dose ICS or LTRA plus as-needed SABA (54%) **Cohort settings:** Start age: 41 (24 to 58) Male: 37.8% Asthma uncontrolled on SABA: 46% Asthma controlled on low-dose ICS or LTRA: 54% **Intervention 1:** Maintenance ICS (budesonide 200 µg) plus as-needed SABA (terbutaline) **Intervention 2:** As-needed combination inhaler ICS/LABA	**Total costs (mean per patient):** Intervention 1: £1,611 Intervention 2: £1,318 Incremental (2−1): saves £293 (95% CI: -£697 to £123; P=NR) **Currency & cost year:** 2018 UK pounds **Cost components incorporated:** Inhalers, system steroids, inpatient hospitalisation, ED, ambulance, GP visit.	**QALYs (mean per patient):** Intervention 1: 18.879 Intervention 2: 18.880 Incremental (2−1): 0.001 (95% CI: -0.001, 0.003 p=NR)	**ICER (Intervention 2 versus Intervention 1):** Dominates (greater QALY gain at a lower cost) Probability that Intervention 2 was cost effective (£20K): 85% **Analysis of uncertainty:** Several one-way and scenario analyses were conducted. The results were found to be sensitive to the following variables: annual exacerbation rates; mean number of inhalation of ICS/LABA and ICS per day; discount rates. In all sensitivity analyses, except for changes in annual exacerbation rates, ICS/LABA dominates ICS plus SABA.

Discounting: Costs: 3.5%; Outcomes: 3.5%	(budesonide/formoterol 200/6 µg)			
Data sources				
Health outcomes: Severe exacerbation rates were collected from SYGMA 2 trial(Bateman et al., 2018) **Quality-of-life weights:** EQ-5D-5L collected from SYGMA 2 trial(Bateman et al., 2018). Disutility values for exacerbations were derived from Lloyd 2007. Disutility value for severe exacerbation requiring ED plus systemic steroid was assumed. **Cost sources:** 2018 BNF for drug acquisition costs, MIMS for cost of system steroids, UK National Tariff for ED visit and ambulance cost, exacerbations requiring hospitalisation from NHS Reference Costs, GP visits from PSSRU.				
Comments				
Source of funding: AstraZeneca funded the study and had a role in study design, data collection, data analysis, data interpretation, and writing of the report. **Limitations:** The analysis was based on SYGMA 2 which included both people who were treatment-naïve and people who were receiving ICS before the enrolment. The clinical review included a post-hoc subgroup analysis on treatment-naïve people from SYGMA 2 in line with the protocol, finding greater benefits of the combination inhaler on this subgroup in terms of severe exacerbations. Hence, this analysis is likely underestimating the benefits of combination inhaler on a treatment-naïve population. Some relevant outcomes, such as asthma control and non-severe exacerbations were not included. These were found to be similar in previous study although SYGMA 2 found non-clinically significant benefits in asthma control and quality of life with ICS plus SABA compared to combination ICS/LABA inhaler. QALYs were calculated using EQ-5D-5L instead of EQ-5D-3L. **Other:**				
Overall applicability:[a] Partially applicable **Overall quality:**[b] Potentially serious limitations				

Abbreviations: BNF= British national formulary; ED= emergency department; EQ-5D-5L= EuroQoL–5 Dimension; ICER= incremental cost-effectiveness ratio; ICS= inhaled corticosteroids; n/a= not available; LABA= long-acting β2-antagonist; LTR = leukotriene receptor antagonists; MIMS= monthly index of medical specialties; PSSRU= personal Social Services Research Unit; QALY= quality-adjusted life years; RCT= randomised controlled trial; SABA= short-acting β2-antagonist.
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Excluded studies

Table 25: Studies excluded from the clinical evidence review

Study	Code [Reason]
Aagaard, L. and Hansen, E. H. (2014) Adverse drug reactions associated with asthma medications in children: systematic review of clinical trials. International Journal of Clinical Pharmacy 36(2): 243-52	- No additional studies identified from review
Agertoft, L. and Pedersen, S. (1994) Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respiratory Medicine 88(5): 373-81	- Study design not relevant to this review protocol
Aldrey, O. E., Anez, H., Deibis, L. et al. (1995) A double-blind, cross-over study using salbutamol, beclomethasone, and a combination of both in bronchial asthma. Journal of Asthma 32(1): 21-8	- Study duration not appropriate for this review protocol
Allen, D. B.; Mullen, M.; Mullen, B. (1994) A meta-analysis of the effect of oral and inhaled corticosteroids on growth. Journal of Allergy & Clinical Immunology 93(6): 967-76	- Study design not relevant to this review protocol
Amar, N. J., Shekar, T., Varnell, T. A. et al. (2017) Mometasone furoate (MF) improves lung function in pediatric asthma: A double-blind, randomized controlled dose-ranging trial of MF metered-dose inhaler. Pediatric Pulmonology 52(3): 310-318	- Population not relevant to this review protocol *Participants were receiving ICS prior to study entry*
Anderson, W., Short, P., Williamson, P. et al. (2012) Effects of inhaled corticosteroids on asthmatic inflammation: the FeNOtype trial. European respiratory journal 40(suppl56): 369sp2088	- Conference abstract
Anonymous (1999) The Childhood Asthma Management Program (CAMP): design, rationale, and methods. Childhood Asthma Management Program Research Group. Controlled Clinical Trials 20(1): 91-120	- Study design not relevant to this review protocol
Anonymous (1996) The START study: inhaled steroid treatment as regular therapy in early asthma. Australian Family Physician 25(11): 1675	- Study design not relevant to this review protocol

Study	Code [Reason]
Anonymous (2007) Inhaled corticosteroids appear to have little risk of causing adverse effects on growth, bone density or cortisol levels in children with asthma. Drugs and Therapy Perspectives 23(7): 21-23	- No additional studies identified from review
Antilla, M., Castro, F., Cruz, A. et al. (2014) Efficacy and safety of the single-capsule combination of fluticasone/formoterol in patients with persistent asthma: a non-inferiority trial. Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia 40(6): 599-608	- Population not relevant to this review protocol
Apold, J. (1975) Treatment of asthma in children with beclomethasone dipropionate aerosols. Tidsskrift for den norske laegeforening 95(1921): 1149-1152	- Study not reported in English
Baggott, C., Hardy, J., Sparks, J. et al. (2020) Self-titration of inhaled corticosteroid and β2-agonist in response to symptoms in mild asthma: a pre-specified analysis from the PRACTICAL randomised controlled trial. The european respiratory journal 56(4)	- Population not relevant to this review protocol
Bareille, P., Tomkins, S., Imber, V. et al. (2020) A randomized, double-blind, placebo-controlled, parallel-group study of once-daily inhaled fluticasone furoate on the hypothalamic-pituitary-adrenocortical axis of children with asthma. Allergy, Asthma, & Clinical Immunology : Official Journal of the Canadian Society of Allergy & Clinical Immunology 16: 11	- No outcomes relevant to this review protocol *Inadequate treatment duration to assess outcomes relevant to this protocol*
Barnes, P. J. (2001) Clinical outcome of adding long-acting beta-agonists to inhaled corticosteroids. Respiratory Medicine 95supplb: S12-6	- Review article but not a systematic review
Barnes, P. J., O'Byrne, P. M., Rodriguez Roisin, R. et al. (2000) Treatment of mild persisitent asthma with low doses of inhaled Budesonide alone or in combination with Formoterol. Thorax 55(suppl3): a4	- Population not relevant to this review protocol
Barrueto, L., Muñoz, T., Aguirre, V. et al. (2002) Quality of life in mothers of infants with asthma. Effect of treatment with inhaled corticosteroid. Enfermedades respir. Cir. Torac 18(4): n	- Study not reported in English

Study	Code [Reason]
Barthwal, M. S. and Meshram, S. (2017) A randomized, double-blind study comparing the efficacy and safety of a combination of formoterol and ciclesonide with ciclesonide alone in asthma subjects with moderate-to-severe airflow limitation. Lung India 34(1): 111-112	- Not a peer-reviewed publication
Bateman, E. D., Esser, D., Chirila, C. et al. (2015) Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: Systematic review and network meta-analysis. Journal of Allergy & Clinical Immunology 136(4): 914-22	- No additional studies identified from review
Bateman, E. D., Reddel, H. K., O'Byrne, P. M. et al. (2018) As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. New England Journal of Medicine 378(20): 1877-1887	- Population not relevant to this review protocol
Beasley, R., Harper, J., Bird, G. et al. (2019) Dose-response relationship of ICS/fast-onset LABA as reliever therapy in asthma. BMC Pulmonary Medicine 19(1): 264	- No additional studies identified from review
Beasley, R., Pavord, I., Papi, A. et al. (2016) Description of a randomised controlled trial of inhaled corticosteroid/fast-onset LABA reliever therapy in mild asthma. European Respiratory Journal 47(3): 981-4	- Study design not relevant to this review protocol
Bennati, D., Piacentini, G. L., Peroni, D. G. et al. (1989) Changes in bronchial reactivity in asthmatic children after treatment with beclomethasone alone or in association with salbutamol. Journal of Asthma 26(6): 359-64	- Study duration not appropriate for this review protocol
Berger, W. E. (2011) Mometasone furoate/formoterol in the treatment of persistent asthma. Expert Review of Respiratory Medicine 5(6): 739-46	- Conference abstract
Berger, W. E. (2004) Efficacy and safety of inhaled corticosteroids in infants and young children with persistent asthma. Allergy and Clinical Immunology International 16(6): 224-230	- No additional studies identified from review

Study	Code [Reason]
Berger, W. E. and Shapiro, G. G. (2004) The use of inhaled corticosteriods for persistent asthma in infants and young children. Annals of Allergy, Asthma and Immunology 92(4): 387-400+463	- Duplicate reference
Berger, W. E., Weinstein, S., Teper, A. et al. (2010) Physical function improvements in children receiving mometasone furoate via a dry-powder inhaler for asthma symptoms: an evaluation of treatment effects from three clinical trials. Chest 138(4): 314a	- Review article but not a systematic review
Bleecker, E. R., Lotvall, J., O'Byrne, P. M. et al. (2014) Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. The Journal of Allergy & Clinical Immunology in Practice 2(5): 553-61	- Population not relevant to this review protocol *Participants were receiving ICS prior to study entry*
Bodzenta-Lukaszyk, A., Pulka, G., Dymek, A. et al. (2011) Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. Respiratory Medicine 105(5): 674-82	- Population not relevant to this review protocol
Bosley, C. M.; Parry, D. T.; Cochrane, G. M. (1994) Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance?. European Respiratory Journal 7(3): 504-9	- Population not relevant to this review protocol
Boulet, L. P., Deschesnes, F., Chaboillez, S. et al. (2010) Protocol: influence of budesonide and budesonide/formoterol on asthma control in smoking asthmatic adults. The Open Respiratory Medicine Journal 4: 51-7	- Study design not relevant to this review protocol
Brand, P. L. (2011) Inhaled corticosteroids should be the first line of treatment for children with asthma. Paediatric Respiratory Reviews 12(4): 245-9	- Review article but not a systematic review
Brand, P. L. P., Duiverman, E. J., Waalkens, H. J. et al. (1999) Peak flow variation in childhood asthma: Correlation with symptoms, airways obstruction, and hyperresponsiveness during long term treatment with inhaled corticosteroids. Thorax 54(2): 103-107	- Population not relevant to this review protocol
Brusselle, G., Nicolini, G., Santoro, L. et al. (2021) Beclometasone dipropionate/formoterol	- Population not relevant to this review protocol

Study	Code [Reason]
maintenance and reliever therapy asthma exacerbation benefit increases with blood eosinophil level. European Respiratory Journal 58(1)	
Buhl, R., Creemers, J. P., Vondra, V. et al. (2001) Once-daily budesonide/formoterol via a single inhaler is effective in mild-to-moderate persistent asthma. European respiratory journal 18(suppl33): 21s	- Population not relevant to this review protocol
Buhl, R., Zetterstrom, O., Mellem, H. et al. (2001) Improved asthma control with budesonide/formoterol via a single inhaler compared with budesonide alone, in moderate persistent asthma. European respiratory journal 18(suppl33): 48s	- Duplicate reference
Busse, W. W., Bateman, E. D., O'Byrne, P. M. et al. (2014) Once-daily fluticasone furoate 50 mcg in mild-to-moderate asthma: a 24-week placebo-controlled randomized trial. Allergy 69(11): 1522-30	- Population not relevant to this review protocol *18% of participants were receiving leukotriene modifying agents prior to study entry*
Busse, W. W., Pedersen, S., Pauwels, R. A. et al. (2008) The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. Journal of Allergy & Clinical Immunology 121(5): 1167-74	- Study design not relevant to this review protocol *Non-randomised follow-up of an RCT*
Camargos, P., Affonso, A., Calazans, G. et al. (2018) On-demand intermittent beclomethasone is effective for mild asthma in Brazil. Clinical and Translational Allergy 8(1)	- Population not relevant to this review protocol
Canadian Agency for, Drugs and Technologies in, Health (2010) Long-acting beta(2)-agonist and inhaled corticosteroid combination therapy for adult persistent asthma: systematic review of clinical outcomes and economic evaluation. CADTH Technology Overviews 1(3): e0120	- No additional studies identified from review
Castro-Rodriguez, J. A.; Custovic, A.; Ducharme, F. M. (2016) Treatment of asthma in young children: evidence-based recommendations. Asthma Research & Practice 2: 5	- Comparator in study does not match that specified in this review protocol
Cates, C. J. and Lasserson, T. J. (2009) Combination formoterol and budesonide as	- No additional studies identified from review

Study	Code [Reason]
maintenance and reliever therapy versus inhaled steroid maintenance for chronic asthma in adults and children. Cochrane Database of Systematic Reviews: cd007313	*Review included studies that contained participants who were not steroid naïve*
Cates, C. J.; Lasserson, T. J.; Jaeschke, R. (2009) Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews: cd006924	- No additional studies identified from review *Review included studies that contained participants who were not steroid naïve*
Cates, C. and Lasserson, T. J. (2008) Combination inhaled steroid and long-acting beta-agonist versus fast-acting beta agonist as relief medication for chronic asthma in adults and children. Cochrane Database of Systematic Reviews	- Duplicate reference
Cates, Cj and Karner, C (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database of Systematic Reviews	- No additional studies identified from review *Review included studies that contained participants that were not steroid naïve*
Cates, Cj and Lasserson, Tj (2009) Combination formoterol and inhaled steroid versus beta2-agonist as relief medication for chronic asthma in adults and children. Cochrane Database of Systematic Reviews	- No additional studies identified from review *Review included studies that contained participants that were not steroid naïve, or had interventions that did not match this review protocol*
Cheng, Q. J., Huang, S. G., Chen, Y. Z. et al. (2016) Formoterol as reliever medication in asthma: a post-hoc analysis of the subgroup of the RELIEF study in East Asia. BMC Pulmonary Medicine 16: 8	- Population not relevant to this review protocol
Chhabra, S. (1994) A comparison of inhaled salbutamol with a combination of salbutamol and beclomethasone dipropionate in moderately severe asthma. Indian journal of chest diseases and allied science 36(3): 119-124	- Study duration not appropriate for this review protocol
Chowdhury, B. A.; Seymour, S. M.; Levenson, M. S. (2011) Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. New England Journal of Medicine 364(26): 2473-5	- Study design not relevant to this review protocol
Cividini, Sofia, Sinha, Ian, Donegan, Sarah et al. (2023) Best step-up treatments for children with	- No additional studies identified from review

Study	Code [Reason]
uncontrolled asthma: A systematic review and network meta-analysis of individual participant data. The European respiratory journal	
Condemi, J. J., Chervinsky, P., Goldstein, M. F. et al. (1997) Fluticasone propionate powder administered through Diskhaler versus triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma. Journal of Allergy & Clinical Immunology 100(4): 467-74	- Population not relevant to this review protocol *Participants had received ICS prior to study entry*
Connett, G. and Lenney, W. (1993) Prevention of viral induced asthma attacks using inhaled budesonide. Archives of Disease in Childhood 68(1): 85-7	- Study does not contain an intervention relevant to this review protocol *Study provided ICS to be used upon onset of respiratory infection symptoms, not as a regular maintenance treatment*
Corren, J., Mansfield, L. E., Pertseva, T. et al. (2013) Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma. Respiratory Medicine 107(2): 180-95	- Population not relevant to this review protocol
Covar, R. A., Fuhlbrigge, A. L., Williams, P. et al. (2012) The Childhood Asthma Management Program (CAMP): Contributions to the Understanding of Therapy and the Natural History of Childhood Asthma. Current Respiratory Care Reports 1(4): 243-250	- Study does not contain an intervention relevant to this review protocol
Crossingham, I., Turner, S., Ramakrishnan, S. et al. (2021) Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma: a Cochrane systematic review. BMJ Evidence based Medicine 19: 19	- Study does not contain an intervention relevant to this review protocol *Review contains studies that used therapeutic options not covered in this review (e.g., Formoterol as a sole therapy)*
Crossingham, I., Turner, S., Ramakrishnan, S. et al. (2021) Combination fixed-dose β agonist and steroid inhaler as required for adults or children with mild asthma: a Cochrane systematic review. BMJ evidence-based medicine	- Systematic review used as source of primary studies
Cusack, R. P.; Satia, I.; O'Byrne, P. M. (2020) Asthma maintenance and reliever therapy: Should this be the standard of care?. Annals of Allergy, Asthma, & Immunology 125(2): 150-155	- Review article but not a systematic review

Study	Code [Reason]
Czarnecka, K. and Chapman, K. R. (2012) The clinical impact of single inhaler therapy in asthma. Clinical & Experimental Allergy 42(7): 1006-13	- Review article but not a systematic review
Danov, Z. and Guilbert, T. (2009) Regular use of inhaled corticosteroids controls symptoms of mild persistent asthma, but with growth effect. Journal of Pediatrics 154(1): 150	- Comparator in study does not match that specified in this review protocol
Deeks, E. D. and Al-Salama, Z. T. (2019) Fluticasone propionate/formoterol fumarate in children aged >= 5 years with asthma: a profile of its use. Drugs and Therapy Perspectives 35(12): 601-606	- Review article but not a systematic review
Deepa Latha, C. and Deshpande, N. (2011) Efficacy of inhaled corticosteroid 'Mometasone furoate (dpi) alone or combined with long acting beta 2 agonist formeterol (DPI) in treatment of chronic asthma. International Journal of Pharmacy and Pharmaceutical Sciences 3(2): 107-108	- Population not relevant to this review protocol
Direkwattanachai, Chalerat, Deerojanawong, Jitladda, Aksilp, Chalermthai et al. (2023) Practical recommendations for home-nebulized corticosteroid use in children aged <= 5 years with asthma: A review and advisory group consensus. Asian Pacific journal of allergy and immunology	- Systematic review used as source of primary studies
Domingo, C.; Rello, J.; Sogo, A. (2019) As-needed ICS-LABA in Mild Asthma: What Does the Evidence Say?. Drugs 79(16): 1729-1737	- Review article but not a systematic review
Eliraz, A., Fritscher, C. C., Perez, C. M. R. et al. (2001) Budesonide and formoterol in a single inhaler quickly gains asthma control compared with fluticasone propionate in mild asthma. European respiratory journal 18(suppl33): 48s	- Conference abstract
Emami, M., Tayebi, A., Gharipour, M. et al. (2014) Comparing clinical efficacy of Symbicort versus Pulmicort in reducing asthma symptom and improving its control. Advanced Biomedical Research 3: 86	- Population not relevant to this review protocol
Fingleton, J., Hardy, J., Baggott, C. et al. (2017) Description of the protocol for the PRACTICAL study: a randomised controlled trial of the	- Study design not relevant to this review protocol

Study	Code [Reason]
efficacy and safety of ICS/LABA reliever therapy in asthma. BMJ open respiratory research 4(1): e000217	
FitzGerald, J. M., O'Byrne, P. M., Bateman, E. D. et al. (2021) Safety of As-Needed Budesonide-Formoterol in Mild Asthma: Data from the Two Phase III SYGMA Studies. Drug Safety 44(4): 467-478	- Population not relevant to this review protocol
Fitzpatrick, A. M., Jackson, D. J., Mauger, D. T. et al (2016) Individualized therapy for persistent asthma in young children. J Allergy Clin Immunol 138(6): 1608-1618.	- Included in review 3.2 (Drug combinations and sequencing) as more closely meets the protocol for that review.
Galant, S. P., van Bavel, J., Finn, A. et al. (1999) Diskus and diskhaler: efficacy and safety of fluticasone propionate via two dry powder inhalers in subjects with mild-to-moderate persistent asthma. Annals of Allergy, Asthma, & Immunology 82(3): 273-80	- Population not relevant to this review protocol *Participants could have been receiving ICS prior to study entry*
Goldsmith, D. R. and Keating, G. M. (2004) Budesonide/formoterol: a review of its use in asthma. Drugs 64(14): 1597-618	- More recent systematic review included that covers the same topic
Goulden, Nia, Cousins, Michael, Hart, Kylie et al. (2022) Inhaled Corticosteroids Alone and in Combination With Long-Acting beta2 Receptor Agonists to Treat Reduced Lung Function in Preterm-Born Children: A Randomized Clinical Trial. JAMA pediatrics 176(2): 133-141	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS to regular ICS/LABA or placebo - regular ICS/LABA not a relevant intervention in this review protocol*
Haahtela, T., Jarvinen, M., Kava, T. et al. (1991) Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. New England Journal of Medicine 325(6): 388-92	- Data not reported in an extractable format or a format that can be analysed
Haahtela, T., Tamminen, K., Malmberg, L. P. et al. (2006) Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: A SOMA study. European Respiratory Journal 28(4): 748-55	- Study does not contain an intervention relevant to this review protocol *Formoterol not included in this review protocol as a sole therapy*
Hambleton, G.; Lewis, H.; Daly, S. (1987) Is the combination inhaler of salbutamol and beclomethasone dipropionate as effective as the same agents from separate inhalers in the management of childhood asthma?. Current Medical Research & Opinion 10(8): 548-54	- Population not relevant to this review protocol

Study	Code [Reason]
Hardy, J., Baggott, C., Fingleton, J. et al. (2019) Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 394(10202): 919-928	- Population not relevant to this review protocol *Participants were not excluded if receiving maintenance ICS at screening*
Hardy, J., Tewhaiti-Smith, J., Baggott, C. et al. (2020) Combination budesonide/formoterol inhaler as sole reliever therapy in Maori and Pacific people with mild and moderate asthma. New Zealand Medical Journal 133(1520): 61-72	- Population not relevant to this review protocol *Participants were not excluded if receiving maintenance ICS at screening*
Hatter, L., Bruce, P., Braithwaite, I. et al. (2021) ICS-formoterol reliever versus ICS and short-acting beta2-agonist reliever in asthma: a systematic review and meta-analysis. Erj Open Research 7(1)	- No additional studies identified from review
Hatter, L., Bruce, P., Holliday, M. et al. (2021) The children's anti-inflammatory reliever (CARE) study: A protocol for a randomised controlled trial of budesonideformoterol as sole reliever therapy in children with mild asthma. ERJ Open Research 7(4)	- Study design not relevant to this review protocol
Hong, J. G., Wandalsen, G., Murphy, K. R. et al. (2020) Nebulized Inhaled Corticosteroids in Asthma Treatment in Children ≤5 Years of Age: A Systematic Review and Global Expert Analysis. The journal of allergy and clinical immunology. In practice	- No additional studies identified from review
Hoshino, M. and Ohtawa, J. (2012) Effects of budesonide/formoterol combination therapy versus budesonide alone on airway dimensions in asthma. Respirology 17(4): 639-46	- Study does not contain an intervention relevant to this review protocol
Imam, SF; Zafar, S; Oppenheimer, J (2022) SMART in treatment of asthma exacerbations. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology	- Systematic review used as source of primary studies
Irani, A. M., Cruz-Rivera, M., Fitzpatrick, S. et al. (2002) Effects of budesonide inhalation suspension on hypothalamic-pituitary-adrenal-axis function in infants and young children with persistent asthma. Annals of Allergy, Asthma, & Immunology 88(3): 306-12	- Review article but not a systematic review

Study	Code [Reason]
Janjua, S, Schmidt, S, Ferrer, M et al. (2019) Inhaled steroids with and without regular formoterol for asthma: serious adverse events. Cochrane Database of Systematic Reviews	- No additional studies identified from review *Review included studies that contained participants who were not steroid naïve*
Jenkins, C., Kolarikova, R., Kuna, P. et al. (2006) Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology 11(3): 276-86	- Population not relevant to this review protocol
Johannessen, H.; Halvorsen, F. J.; Kommedal, T. M. (1975) Beclomethasone dipropionate aerosol in adult steroid independent patients with perennial bronchial asthma. Current Therapeutic Research, Clinical & Experimental 18(4): 559-67	- Population not relevant to this review protocol
Jorup, C.; Lythgoe, D.; Bisgaard, H. (2018) Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. European Respiratory Journal 51(1): 01	- Population not relevant to this review protocol
Kanniess, F., Scuri, M., Vezzoli, S. et al. (2015) Extrafine beclomethasone/formoterol combination via a dry powder inhaler (NEXThaler) or pMDI and beclomethasone monotherapy for maintenance of asthma control in adult patients: A randomised, double-blind trial. Pulmonary Pharmacology and Therapeutics 30: 121-127	- Population not relevant to this review protocol
Karaman, O., Arli, O., Uzuner, N. et al. (2007) The effectiveness of asthma therapy alternatives and evaluating the effectivity of asthma therapy by interleukin-13 and interferon gamma levels in children. Allergy & Asthma Proceedings 28(2): 204-9	- Study does not contain an intervention relevant to this review protocol
Kardos, P. (2013) Budesonide/formoterol maintenance and reliever therapy versus free-combination therapy for asthma: a real-life study. Pneumologie 67(8): 463-70	- Population not relevant to this review protocol
Kelly, M. M., O'Connor, T. M., Leigh, R. et al. (2010) Effects of budesonide and formoterol on allergen-induced airway responses, inflammation, and airway remodeling in asthma. Journal of Allergy & Clinical Immunology 125(2): 349-356.e13	- No outcomes relevant to this review protocol

Study	Code [Reason]
Kerrebijn, K. F.; van Essen-Zandvliet, E. E.; Neijens, H. J. (1987) Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. Journal of Allergy & Clinical Immunology 79(4): 653-9	- Comparator in study does not match that specified in this review protocol
Kerstjens, H. A. M., Postma, D. S., Van Doormaal, J. J. et al. (1994) Effects of short term and long term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. Thorax 49(7): 652-656	- Comparator in study does not match that specified in this review protocol
Kerwin, E. M., Gillespie, M., Song, S. et al. (2017) Randomized, dose-ranging study of a fluticasone propionate multidose dry powder inhaler in adolescents and adults with uncontrolled asthma not previously treated with inhaled corticosteroids. Journal of Asthma 54(1): 89-98	- Population not relevant to this review protocol *Participants could have been receiving ICS prior to study entry*
Kew, Km, Karner, C, Mindus, Sm et al. (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database of Systematic Reviews	- No additional studies identified from review *Review included studies that contained participants that were not steroid naïve*
Kim, Y. Y.; Cho, S. H.; Min, K. U. (1997) Efficacy and safety of budesonide turbuhaler in Korean asthmatic patients. Korean journal of allergy 17(1): 49-57	- Full text paper not available
Kooi, E. M., Schokker, S., Marike Boezen, H. et al. (2008) Fluticasone or montelukast for preschool children with asthma-like symptoms: Randomized controlled trial. Pulmonary Pharmacology & Therapeutics 21(5): 798-804	- Data not reported in an extractable format or a format that can be analysed
Korenblat, P. E. and Rosenwasser, L. J. (2010) Budesonide/formoterol pressurized metered-dose inhaler for patients with persistent asthma. Allergy & Asthma Proceedings 31(3): 190-202	- Review article but not a systematic review
Kovesi, T. (2011) In children and adolescents with mild persistent asthma, daily beclomethasone reduces treatment failure compared with rescue beclomethasone plus albuterol. Evidence-Based Medicine 16(6): 183-184	- Study design not relevant to this review protocol

Study	Code [Reason]
Kowalski, M. L., Wojciechowski, P., Dziewonska, M. et al. (2016) Adrenal suppression by inhaled corticosteroids in patients with asthma: A systematic review and quantitative analysis. Allergy & Asthma Proceedings 37(1): 9-17	- No additional studies identified from review
Kudo, K.; Hojo, M.; Kabe, J. (1995) Inhaled beclomethasone in long-term management of asthma: optimal dose and optimal duration of treatment. Nihon Kyobu Shikkan Gakkai zasshi 33(9): 956-965	- Study not reported in English
Kuna, P., Chuchalin, A., Ringdal, N. et al. (2001) Low-dose single-inhaler budesonide/formoterol administered once daily is effective in mild-persistent asthma. European respiratory journal 18(suppl33): 158s	- Conference abstract
La Rosa, M., Francesco, G., Musarra, I. et al. (1991) Double-blind comparative study of inhaled flunisolide and flunisolide plus salbutamol in bronchial asthma in children. Current Therapeutic Research - Clinical and Experimental 50(1): 56-61	- Comparator in study does not match that specified in this review protocol
Laforce, C., Meltzer, E. O., Nathan, R. A. et al. (2011) Greater reduction in asthma symptom frequency during treatment with mometasone furoate/formoterol combination versus monocomponents and placebo. Journal of allergy and clinical immunology 127(2suppl1): ab158	- Population not relevant to this review protocol
Laitinen, L. A.; Laitinen, A.; Haahtela, T. (1992) A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta 2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. Journal of Allergy & Clinical Immunology 90(1): 32-42	- Comparator in study does not match that specified in this review protocol
Li, S., Mei, Q., Qian, D. et al. (2021) Salbutamol combined with budesonide in treatment of pediatric bronchial asthma and its effect on eosinophils. Minerva Pediatrics 73(3): 215-221	- Study does not contain an intervention relevant to this review protocol
Li, Z. Y., Lin, T. Y., Wu, F. et al. (2003) Effect of terbutaline on bronchial inflammation in asthma patients who inhaled budesonide. Chinese journal of clinical pharmacy 12(6): nil0002	- Study not reported in English

Study	Code [Reason]
Liu, T.; Yang, D.; Liu, C. (2021) Extrafine HFA-beclomethasone-formoterol vs. nonextrafine combination of an inhaled corticosteroid and a long acting beta2-agonist in patients with persistent asthma: A systematic review and meta-analysis. PLoS ONE [Electronic Resource] 16(9): e0257075	- No additional studies identified from review
Loke, Y. K., Gilbert, D., Thavarajah, M. et al. (2015) Bone mineral density and fracture risk with long-term use of inhaled corticosteroids in patients with asthma: systematic review and meta-analysis. BMJ Open 5(11): e008554	- No additional studies identified from review
Lotvall, J., Bleecker, E. R., Busse, W. W. et al. (2014) Efficacy and safety of fluticasone furoate 100 mug once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. Respiratory Medicine 108(1): 41-9	- Population not relevant to this review protocol *Participants were receiving ICS prior to study entry*
Loymans, R. J., Gemperli, A., Cohen, J. et al. (2014) Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. BMJ 348: g3009	- No additional studies identified from review
Main, C., Shepherd, J., Anderson, R. et al. (2008) Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. Health Technology Assessment (Winchester, England) 12(20): 1-174, iii	- No additional studies identified from review
Malmstrom, K., Rodriguez-Gomez, G., Guerra, J. et al. (1999) Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: A randomized, controlled trial. Annals of Internal Medicine 130(6): 487-495	- Population not relevant to this review protocol *>10% of participants were receiving maintenance therapies other than ICS at baseline*
Mangunnegoro, H. (1998) Cost effectiveness of the addition of inhaled corticosteroid in moderately persistent asthmatics treated with daily oral bronchodilator. Medical Journal of Indonesia 7(4): 251-256	- Study does not contain an intervention relevant to this review protocol
Mapel, D. W. and Roberts, M. H. (2014) Management of asthma and chronic obstructive pulmonary disease with combination inhaled corticosteroids and long-acting beta-agonists: a	- Comparator in study does not match that specified in this review protocol

Study	Code [Reason]
review of comparative effectiveness research. Drugs 74(7): 737-55	
Mapel, D. W.; Roberts, M. H.; Davis, J. (2020) Budesonide/formoterol therapy: Effective and appropriate use in asthma and chronic obstructive pulmonary disease. Journal of Comparative Effectiveness Research 9(4): 231-251	- No additional studies identified from review
Martinez, F. D., Chinchilli, V. M., Morgan, W. J. et al. (2011) Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet 377(9766): 650-7	- Comparator in study does not match that specified in this review protocol
Matsunaga, K., Kawabata, H., Hirano, T. et al. (2013) Difference in time-course of improvement in asthma control measures between budesonide and budesonide/formoterol. Pulmonary Pharmacology & Therapeutics 26(2): 189-94	- Comparator in study does not match that specified in this review protocol
McDonald, C.; Pover, G. M.; Crompton, G. K. (1988) Evaluation of the combination inhaler of salbutamol and beclomethasone dipropionate in the management of asthma. Current Medical Research & Opinion 11(2): 116-22	- Population not relevant to this review protocol
Meltzer, E. O., Pearlman, D. S., Eckerwall, G. et al. (2015) Efficacy and safety of budesonide administered by pressurized metered-dose inhaler in children with asthma. Annals of Allergy, Asthma, & Immunology 115(6): 516-22	- Population not relevant to this review protocol *Participants were receiving controller medication prior to study entry*
Molitor, S.; Liefring, E.; Trautmann, M. (2005) Asthma control with the salmeterol-fluticasone-combination disc compared to standard treatment. Pneumologie (Stuttgart, Germany) 59(3): 167-173	- Study not reported in English
Morice, A. H. and Taylor, M. E. (1999) A randomised trial of the initiation of asthma treatment. Asthma in General Practice 7(1): 7-9	- Study duration not appropriate for this review protocol
Mukhopadhyay, A., Waked, M., Gogtay, J. et al. (2020) Comparing the efficacy and safety of formoterol/budesonide pMDI versus its mono-components and other LABA/ICS in patients with asthma. Respiratory Medicine 170: 106055	- No additional studies identified from review

Study	Code [Reason]
Muraki, M., Gose, K., Hanada, S. et al. (2017) Which inhaled corticosteroid and long-acting b-agonist combination is better in patients with moderate-to-severe asthma, a dry powder inhaler or a pressurized metered-dose inhaler?. Drug Delivery 24(1): 1395-1400	- Population not relevant to this review protocol
Murphy, K. R., Hong, J. G., Wandalsen, G. et al. (2020) Nebulized Inhaled Corticosteroids in Asthma Treatment in Children 5 Years or Younger: A Systematic Review and Global Expert Analysis. The Journal of Allergy & Clinical Immunology in Practice 8(6): 1815-1827	- Systematic review used as source of primary studies
Murphy, K. R., Uryniak, T., Martin, U. J. et al. (2012) The effect of budesonide/formoterol pressurized metered-dose inhaler on predefined criteria for worsening asthma in four different patient populations with asthma. Drugs in R & D 12(1): 9-14	- Secondary analysis of excluded studies
Murphy, K., Nelson, H., Parasuraman, B. et al. (2008) The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. Current Medical Research & Opinion 24(3): 879-94	- Population not relevant to this review protocol
Nam, T. H., Kang, S. Y., Lee, S. M. et al. (2022) Comparison of Two pMDIs in Adult Asthmatics: A Randomized Double-Blind Double-Dummy Clinical Trial. Tuberculosis & Respiratory Diseases 85(1): 25-36	- Population not relevant to this review protocol *Participants were receiving ICS/LABA prior to study entry*
Ni Chroinin, M., Greenstone, I., Lasserson, T. J. et al. (2009) Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database of Systematic Reviews: cd005307	- No additional studies identified from review *Review included studies that compared regular ICS with regular ICS/LABA, which was not a relevant comparison in this review*
Ni Chroinin, M., Greenstone, I., Lasserson, T. J. et al. (2009) Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database of Systematic Reviews 2009(4)	- Duplicate reference
Ni Chroinin, M., Lasserson, T. J., Greenstone, I. et al. (2009) Addition of long-acting beta-agonists to inhaled corticosteroids for chronic	- Duplicate reference

Study	Code [Reason]
asthma in children. Cochrane Database of Systematic Reviews: cd007949	
Ni, C. M.; Greenstone, I. R.; Ducharme, F. M. (2005) Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. Cochrane Database of Systematic Reviews: cd005307	- No additional studies identified from review
Noonan, M., Rosenwasser, L. J., Martin, P. et al. (2006) Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. Drugs 66(17): 2235-54	- Population not relevant to this review protocol
O'Byrne, P. M., Barnes, P. J., Rodriguez-Roisin, R. et al. (2001) Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. American Journal of Respiratory & Critical Care Medicine 164(8pt1): 1392-7	- Study does not contain an intervention relevant to this review protocol
O'Byrne, P. M., Bisgaard, H., Godard, P. P. et al. (2005) Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. American Journal of Respiratory & Critical Care Medicine 171(2): 129-36	- Population not relevant to this review protocol *Participants were receiving ICS prior to study entry*
O'Byrne, P. M., FitzGerald, J. M., Bateman, E. D. et al. (2018) Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. New England Journal of Medicine 378(20): 1865-1876	- Population not relevant to this review protocol
Oliver, A. J., Covar, R. A., Goldfrad, C. H. et al. (2016) Randomized Trial of Once-Daily Fluticasone Furoate in Children with Inadequately Controlled Asthma. Journal of Pediatrics 178: 246-253.e2	- Population not relevant to this review protocol *Participants could have been receiving controller medication prior to study entry*
Overbeek, S. E., Mulder, P. G., Baelemans, S. M. et al. (2005) Formoterol added to low-dose budesonide has no additional antiinflammatory effect in asthmatic patients. Chest 128(3): 1121-7	- Population not relevant to this review protocol
Papi, A., Canonica, G. W., Maestrelli, P. et al. (2007) Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma.	- Population not relevant to this review protocol

Study	Code [Reason]
New England Journal of Medicine 356(20): 2040-52	*4-week run-in period on ICS meant that participants were not treatment naïve at randomisation*
Papi, A., Marku, B., Scichilone, N. et al. (2015) Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. The Lancet Respiratory Medicine 3(2): 109-119	- Population not relevant to this review protocol
Papi, A., Paggiaro, P. L., Nicolini, G. et al. (2007) Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. European Respiratory Journal 29(4): 682-9	- Population not relevant to this review protocol
Parasuramalu, B. G., Sathish Chandra, M. R., Huliraj, N. et al. (2015) Randomized, open label, active controlled study to assess and compare health related quality of life with mometasone & formoterol versus fluticasone & formoterol dry powder inhaler in mild to moderate persistent asthma. Asian Journal of Pharmaceutical and Clinical Research 8(4): 296-298	- Full text paper not available
Park, Hyung Jun, Huh, Jin-Young, Lee, Ji Sung et al. (2022) Comparative efficacy of inhalers in mild-to-moderate asthma: systematic review and network meta-analysis. Scientific reports 12(1): 5949	- Systematic review used as source of primary studies
Patel, M., Pilcher, J., Pritchard, A. et al. (2013) Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. The Lancet Respiratory Medicine 1(1): 32-42	- Population not relevant to this review protocol
Patel, Vithi Hitendra, Thannir, Srijani, Dhanani, Maulik et al. (2023) Current Limitations and Recent Advances in the Management of Asthma. Disease-a-month : DM 69(7): 101483	- Population not relevant to this review protocol *Participants could have received treatments other than SABA prior to study entry (10% theophylline users)*
Pauwels, R. A., Pedersen, S., Busse, W. W. et al. (2003) Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 361(9363): 1071-6	- Population not relevant to this review protocol *>10% of participants were receiving drugs other than SABA prior to randomisation (~5% receiving ICS, ~4% receiving systemic corticosteroids, ~3% receiving LABAs, ~11% receiving xanthines, ~7% receiving*

Study	Code [Reason]
	cromoglicate, ~12% receiving 'other' medications)
Pearlman, D. S.; LaForce, C. F.; Kaiser, K. (2013) Fluticasone/Formoterol combination therapy compared with monotherapy in adolescent and adult patients with mild to moderate asthma. Clinical Therapeutics 35(7): 950-66	- Population not relevant to this review protocol
Pertseva, T.; Dissanayake, S.; Kaiser, K. (2013) Superiority of fluticasone propionate/formoterol fumarate versus fluticasone propionate alone in patients with moderate-to-severe asthma: a randomised controlled trial. Current Medical Research & Opinion 29(10): 1357-69	- Population not relevant to this review protocol
Peters, S. P., Bleecker, E. R., Canonica, G. W. et al. (2016) Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. New England Journal of Medicine 375(9): 850-60	- Population not relevant to this review protocol
Pilcher, J., Patel, M., Smith, A. et al. (2014) Combination budesonide/formoterol inhaler as maintenance and reliever therapy in Maori with asthma. Respirology 19(6): 842-51	- Population not relevant to this review protocol
Plit, M. and Pover, G. M. (1984) Assessment of a new combination inhaler containing salbutamol and beclomethasone dipropionate in the management of asthmatic patients. South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde 65(19): 758-62	- Population not relevant to this review protocol
Ploszczuk, A., Bosheva, M., Spooner, K. et al. (2018) Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial. Therapeutic Advances in Respiratory Disease 12: 1753466618777924	- Population not relevant to this review protocol
Pohl, W. R., Vetter, N., Zwick, H. et al. (2006) Adjustable maintenance dosing with budesonide/formoterol or budesonide: double-blind study. Respiratory Medicine 100(3): 551-60	- Study does not contain an intervention relevant to this review protocol
Pohunek, P., Kuna, P., Jorup, C. et al. (2006) Budesonide/formoterol improves lung function compared with budesonide alone in children	- Population not relevant to this review protocol

Study	Code [Reason]
with asthma. Pediatric Allergy & Immunology 17(6): 458-65	
Pohunek, P., Varoli, G., Reznichenko, Y. et al. (2021) Bronchodilating effects of a new beclometasone dipropionate plus formoterol fumarate formulation via pressurized metered-dose inhaler in asthmatic children: a double-blind, randomized, cross-over clinical study. European Journal of Pediatrics 180(5): 1467-1475	- Population not relevant to this review protocol
Reddel, H. K., Busse, W. W., Pedersen, S. et al. (2017) Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet 389(10065): 157-166	- Population not relevant to this review protocol *Primary study excluded*
Reddel, H. K., O'Byrne, P. M., FitzGerald, J. M. et al. (2021) Efficacy and Safety of As-Needed Budesonide-Formoterol in Adolescents with Mild Asthma. The Journal of Allergy & Clinical Immunology in Practice 9(8): 3069-3077.e6	- Population not relevant to this review protocol
Remington, T. L.; Heaberlin, A. M.; DiGiovine, B. (2002) Combined budesonide/formoterol turbuhaler treatment of asthma. Annals of Pharmacotherapy 36(12): 1918-28	- Review article but not a systematic review
Rico-Mendez, F. G., Ochoa, G., Rocio Chapela, M. et al. (1999) Formoterol dry powder twice daily versus salbutamol aerosol 4 times daily in patients with stable asthma. Revista alergia 262exico 46(5): 130-135	- Study not reported in English
Rico-Méndez, F. G., Ochoa, G., Rocío Chapela, M. et al. (1999) Dry powdered formoterol, twice a day versus aerosolized salbutamol, four times a day, in patients with stable asthma. Revista alergia Mexico (Tecamachalco, Puebla, Mexico : 1993) 46(5): 130-135	- Duplicate reference
Riemersma, R. A.; Postma, D.; van der Molen, T. (2012) Budesonide/formoterol maintenance and reliever therapy in primary care asthma management: effects on bronchial hyperresponsiveness and asthma control. Primary Care Respiratory Journal 21(1): 50-6	- Population not relevant to this review protocol
Rodrigo, G. J., Moral, V. P., Marcos, L. G. et al. (2009) Safety of regular use of long-acting beta	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. Pulmonary Pharmacology & Therapeutics 22(1): 9-19	
Rodriguez-Martinez, Carlos E; Sossa-Briceno, Monica P; Buendia, Jefferson Antonio (2022) As-Needed Use of Short-Acting beta2-Agonists Alone Versus As-Needed Use of Short-Acting beta2-Agonists Plus Inhaled Corticosteroids in Pediatric Patients With Mild Intermittent (Step 1) Asthma: A Cost-Effectiveness Analysis. The journal of allergy and clinical immunology. In practice 10(6): 1562-1568	- No outcomes relevant to this review protocol
Rogliani, P., Beasley, R., Cazzola, M. et al. (2021) SMART for the treatment of asthma: A network meta-analysis of real-world evidence. Respiratory Medicine 188: 106611	- No additional studies identified from review
Rogliani, P.; Ritondo, B. L.; Calzetta, L. (2021) Triple therapy in uncontrolled asthma: a network meta-analysis of phase III studies. European Respiratory Journal 58(3): 09	- Study does not contain an intervention relevant to this review protocol
Rosenhall, L., Elvstrand, A., Tilling, B. et al. (2003) One-year safety and efficacy of budesonide/formoterol in a single inhaler (Symbicort Turbuhaler) for the treatment of asthma. Respiratory Medicine 97(6): 702-8	- Population not relevant to this review protocol
Rosenhall, L., Heinig, J. H., Lindqvist, A. et al. (2002) Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. International Journal of Clinical Practice 56(6): 427-33	- Population not relevant to this review protocol
Salpeter, S. R.; Wall, A. J.; Buckley, N. S. (2010) Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. American Journal of Medicine 123(4): 322-8.e2	- No additional studies identified from review
Samson MA PS (2012) Effectiveness and safety of budesonide alone versus budesonide/formoterol in decreasing the number of severe exacerbations: a randomised controlled trial. Respirology 4: 152	- Full text paper not available
Santus, P., Giovannelli, F., Di Marco, F. et al. (2010) Budesonide/formoterol dry powder in asthma: an option for control as maintenance	- No additional studies identified from review

Study	Code [Reason]
and reliever therapy. Expert Opinion on Pharmacotherapy 11(2): 257-67	
Sears, M. R., Boulet, L. P., Laviolette, M. et al. (2008) Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. European Respiratory Journal 31(5): 982-9	- Population not relevant to this review protocol
Sheffer, A. L., Silverman, M., Woolcock, A. J. et al. (2005) Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. Annals of Allergy, Asthma, & Immunology 94(1): 48-54	- Population not relevant to this review protocol *Participants could have been receiving ICS prior to study entry*
Shepherd, J., Rogers, G., Anderson, R. et al. (2008) Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. Health Technology Assessment (Winchester, England) 12(19): iii-iv, 1	- Duplicate reference
Shimoda, T., Obase, Y., Kishikawa, R. et al. (2016) Assessment of anti-inflammatory effect from addition of a long-acting beta-2 agonist to inhaled corticosteroid. Allergy & Asthma Proceedings 37(5): 387-93	- Study does not contain an intervention relevant to this review protocol
Sileem, A. E., Ali, A., Elnahas, H. et al. (2021) Comparing the asthma control and anti-inflammatory effects of different fixed combinations of inhaled corticosteroids plus long-acting beta 2 agonist; a randomized clinical trial. Open Access Macedonian Journal of Medical Sciences 9(B): 771-778	- Comparator in study does not match that specified in this review protocol
Soes-Petersen, U., Kava, T., Dahle, R. et al. (2011) Budesonide/formoterol maintenance and reliever therapy versus conventional best standard treatment in asthma in an attempted 'real life' setting. The clinical respiratory journal 5(3): 173-82	- Population not relevant to this review protocol
Sriprasart, Thitiwat, Waterer, Grant, Garcia, Gabriel et al. (2023) Safety of SABA Monotherapy in Asthma Management: a Systematic Review and Meta-analysis. Advances in therapy 40(1): 133-158	- Systematic review used as source of primary studies

Study	Code [Reason]
Stallberg, B., Ekstrom, T., Neij, F. et al. (2008) A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. Respiratory Medicine 102(10): 1360-70	- Population not relevant to this review protocol
Sumino, K., Bacharier, L. B., Taylor, J. et al. (2020) A Pragmatic Trial of Symptom-Based Inhaled Corticosteroid Use in African-American Children with Mild Asthma. The Journal of Allergy & Clinical Immunology in Practice 8(1): 176-185.e2	- Population not relevant to this review protocol
Tashkin, D. P., Trudo, F., DePietro, M. et al. (2015) Effect of fixed airflow obstruction (FAO) status on lung function, asthma control days (ACD), and asthma symptom score (AS) responses to budesonide/formoterol (BUD/FM) treatment in patients with moderate-to-severe asthma. Journal of allergy and clinical immunology 135(2suppl1): ab5	- Conference abstract
Taskar, V. S., Mahashur, A. A., John, P. J. et al. (1993) Anti-inflammatory action of steroid inhalers. Journal of the Association of Physicians of India 41(5): 281-3	- Population not relevant to this review protocol
Tattersfield, A. E., Town, G. I., Johnell, O. et al. (2001) Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax 56(4): 272-8	- Comparator in study does not match that specified in this review protocol
Teper, A., Murphy, K. R., Meltzer, E. O. et al. (2010) Reduction of Relief Medication Use in Children Receiving Inhaled Mometasone Furoate for Control of Mild Persistent Asthma. Journal of allergy and clinical immunology 125(2suppl1): ab195	- Conference abstract
Urs, R.C., Evans, D.J., Bradshaw, T.K. et al. (2023) Inhaled corticosteroids to improve lung function in children (aged 6-12 years) who were born very preterm (PICSI): a randomised, double-blind, placebo-controlled trial. The Lancet Child and Adolescent Health 7(8): 567-576	- Population not relevant to this review protocol *Asthma diagnosis was not an inclusion criteria*
van Essen-Zandvliet, E. E., Hughes, M. D., Waalkens, H. J. et al. (1992) Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway	- Population not relevant to this review protocol

Study	Code [Reason]
responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. American Review of Respiratory Disease 146(3): 547-54	
Vandewalker, M.; Hickey, L.; Small, C. J. (2017) Efficacy and safety of beclomethasone dipropionate breath-actuated or metered-dose inhaler in pediatric patients with asthma. Allergy & Asthma Proceedings 38(5): 354-364	- Population not relevant to this review protocol *Participants could have been receiving ICS or other controller medications prior to study entry*
Waalkens, H. J., Gerritsen, J., Koeter, G. H. et al. (1991) Budesonide and terbutaline or terbutaline alone in children with mild asthma: effects on bronchial hyperresponsiveness and diurnal variation in peak flow. Thorax 46(7): 499-503	- Study does not contain an intervention relevant to this review protocol
Waalkens, H. J., Gerrtsen, J., Van Aalderen, W. M. C. et al. (1990) Diurnal variation in peak flow rate in children with mild asthma. Effects of treatment with budesonide and terbutaline. Annual Review of Chronopharmacology 7: 305-308	- Duplicate reference
Wallin, A., Sandstrom, T., Soderberg, M. et al. (1999) The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. American Journal of Respiratory & Critical Care Medicine 159(1): 79-86	- Comparator in study does not match that specified in this review protocol
Wang, G., Zhang, X., Zhang, H. P. et al. (2017) Corticosteroid plus beta2-agonist in a single inhaler as reliever therapy in intermittent and mild asthma: a proof-of-concept systematic review and meta-analysis. Respiratory Research 18(1): 203	- No additional studies identified from review
Weinstein, C. L. J., Ryan, N., Shekar, T. et al. (2019) Serious asthma events with mometasone furoate plus formoterol compared with mometasone furoate. Journal of Allergy & Clinical Immunology 143(4): 1395-1402	- Population not relevant to this review protocol
Weiss, K. B., Liljas, B., Schoenwetter, W. et al. (2004) Effectiveness of budesonide administered via dry-powder inhaler versus triamcinolone acetonide administered via pressurized metered-dose inhaler for adults with persistent asthma in managed care settings. Clinical Therapeutics 26(1): 102-14	- Population not relevant to this review protocol

Study	Code [Reason]
Weiss, K. B., Paramore, L. C., Liljas, B. et al. (2005) Patient satisfaction with budesonide TurbuhalerTM versus triamcinolone acetonide administered via pressurized metered-dose inhaler in a managed care setting. Journal of Asthma 42(9): 769-776	- Population not relevant to this review protocol
Wilson, S. J., Wallin, A., Della-Cioppa, G. et al. (2001) Effects of budesonide and formoterol on NF-kappaB, adhesion molecules, and cytokines in asthma. American Journal of Respiratory & Critical Care Medicine 164(6): 1047-52	- Study does not contain an intervention relevant to this review protocol
Yang, X., Huang, J., Hu, Y. et al. (2020) The rescue intervention strategy for asthma patients under severe air pollution: a protocol for a single-centre prospective randomized controlled trial. Trials [Electronic Resource] 21(1): 912	- Study design not relevant to this review protocol
Yang, X., Huang, J., Hu, Y. et al. (2021) The rescue intervention strategy for asthma patients under severe air pollution: a single-center prospective randomized controlled trial. Journal of Asthma: 1-10	- Population not relevant to this review protocol
Zhang, L; Prietsch, Som; Ducharme, Fm (2014) Inhaled corticosteroids in children with persistent asthma: effects on growth. Cochrane Database of Systematic Reviews	- No additional studies identified from review *Review included studies that contained interventions that were not relevant to this review protocol e.g., placebo, nedocromil sodium*
ZuWallack, R., Adelglass, J., Clifford, D. P. et al. (2000) Long-term efficacy and safety of fluticasone propionate powder administered once or twice daily via inhaler to patients with moderate asthma. Chest 118(2): 303-12	- Population not relevant to this review protocol *Participants had received ICS prior to study entry*

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 26: Studies excluded from the health economic review

Reference	Reason for exclusion
Buendia 2021(Buendia et al., 2021)	Selectively excluded as a more applicable analysis(FitzGerald et al., 2020) conducted from an UK NHS perspective and based on the same RCT was available.

Reference	Reason for exclusion
Briggs 2006(Briggs et al., 2006)	Excluded as rated not applicable. The study looked at the cost-effectiveness of including salmeterol in asthma therapy which was not included as a relevant LABA in the protocol.
Doull 2007(Doull et al., 2007)	Excluded as rated not applicable. The study looked at the cost-effectiveness of including salmeterol in asthma therapy which was not included as a relevant LABA in the protocol.
Miyagawa 2006(Miyagawa et al., 2006)	Excluded as rated not applicable. The study looked at the cost-effectiveness of including salmeterol in asthma therapy which was not included as a relevant LABA in the protocol.
Sadatsafavi 2021(Sadatsafavi et al., 2021)	Selectively excluded as a more applicable analysis(FitzGerald et al., 2020) conducted from an UK NHS perspective and based on the same RCT was available.

Appendix J – Research recommendation

J.1.1 Research recommendation

What is the clinical and cost-effectiveness of regular 'fixed-dose' inhaled corticosteroid (ICS) regimes (using SABA as a reliever) compared with 'as-needed' strategies (for example ICS/formoterol) as the initial standard treatment for asthma in children aged 5-11 years?

J.1.2 Why this is important

Asthma is a common condition that commonly causes attacks, with resultant loss of time in school, anxiety about symptoms, emergency treatment, hospital admission and occasionally, death. Understanding what are the most effective therapies in children should minimise these adverse outcomes. Regular ICS using a "fixed dose" regime may lead to some children with mild, well controlled asthma having a larger cumulative steroid dose than they need.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	There is lack of evidence about the most appropriate initial pharmacological treatment for children with asthma. Despite an increasing adoption of both ICS/Formoterol Maintenance and Reliever Therapy (MART) and Anti-inflammatory Reliever Therapy (AIR) in young people and adults, there is little evidence in children aged 5-11yrs.
Relevance to NICE guidance	"MART" and "AIR" regimes are recommended in young people >12yrs and adults, however there is no evidence with which to make a recommendation in younger children.
Relevance to the NHS	Improvements in initial treatment for children with asthma may result in fewer attacks, thereby reducing the impact of asthma on acute medical services.
National priorities	High
Current evidence base	Minimal data available
Equality considerations	None known

J.1.4 Modified PICO table

Population	Children aged 5-11yrs with a diagnosis of asthma
Intervention	ICS/Formoterol therapy as required as initial therapy
Comparator	Fixed dose ICS with separate SABA as required
Outcome	Impact on attacks, symptoms, hospitalisations and deaths
Study design	Randomised controlled trial
Timeframe	12 months

Additional information	Comparison of adverse events e.g. height velocity, overall steroid use and quality of life would be important to study